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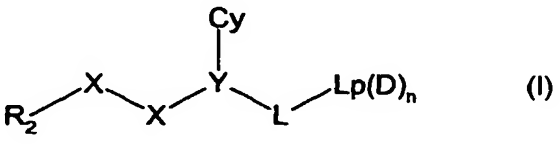


(I)

(57) Abstract: Use of compounds of formula (I) where R_2, each X, L, Y, Cy, Lp, D and n are as defined in the specification, as serine protease inhibitors.

Compounds

This invention relates to compounds that are inhibitors of serine proteases. More particularly, it relates to their use as serine protease inhibitors in the treatment of the human or animal body.

The serine proteases are a group of proteolytic enzymes which have a common catalytic mechanism characterized by a particularly reactive Ser residue. Examples of serine proteases include trypsin, tryptase, chymotrypsin, elastase, thrombin, plasmin, kallikrein, Complement C1, acrosomal protease, lysosomal protease, cocoonase, α-lytic protease, protease A, protease B, serine carboxypeptidase II, subtilisin, urokinase, Factor VIIa, Factor IXa, and Factor Xa. The serine proteases have been investigated extensively over a period of several decades and the therapeutic value of inhibitors of serine proteases is well understood. (For a recent review, see, for example, Donmienne Leung et al., J. Med. Chem., Vol. 43, No. 3, 2000, pages 305-341).

Serine protease inhibitors play a central role in the regulation of a wide variety of physiological processes including coagulation, fibrinolysis, fertilization, development, malignancy, neuromuscular patterning and inflammation. It is well known that these compounds inhibit a variety of circulating proteases as well as proteases that are activated or released in tissue. It is also becoming clear that serine protease inhibitors inhibit critical cellular processes, such as adhesion, migration, free radical production and apoptosis. In addition, animal experiments indicate that intravenously administered serine protease inhibitors, variants or cells expressing serine

protease inhibitors, provide a protective effect against tissue damage.

Serine protease inhibitors have also been predicted to have potential beneficial uses in the treatment of disease in a wide variety of clinical areas such as oncology, neurology, haematology, pulmonary medicine, immunology, inflammation and infectious disease.

In particular serine protease inhibitors may be beneficial in the treatment of thrombotic diseases, asthma, emphysema, cirrhosis, arthritis, carcinoma, melanoma, restenosis, atheroma, trauma, shock and reperfusion injury.

Thus for example an inhibitor of Factor Xa has value as a therapeutic agent as an anticoagulant, e.g. in the treatment and prevention of thrombotic disorders. The use of a Factor Xa inhibitor as an anticoagulant is desirable in view of the selectivity of its effect. Many clinically approved anticoagulants have been associated with adverse events owing to the non-specific nature of their effects on the coagulation cascade.

Also, there are well-known associations of α1 protease inhibitor deficiency with emphysema and cirrhosis and C1 esterase inhibitor deficiency with angioedema.

Tryptase is the major secretory protease of human mast cells and is proposed to be involved in neuropeptide processing and tissue inflammation.

Mature human tryptase is a glycosylated, heparin-associated tetramer of catalytically active subunits. Its amino-acid structure appears to have no close counterpart among the other serine proteases which have been characterised. Tryptase is stored in mast cell secretory granules and after mast cell activation, human tryptase can be measured readily in a variety of biological fluids. For

example, after anaphylaxis, tryptase appears in the blood stream where it is readily detectable for several hours. Tryptase also appears in samples of nasal and lung lavage fluid from atopic subjects challenged with specific antigen. Tryptase has been implicated in a variety of biological processes where activation and degranulation of mast cells occur. Accordingly, mast cell tryptase inhibition may be of great value in the prophylaxis and treatment of a variety of mast cell mediated conditions. Mast cells can degranulate by both IgE-dependent and independent mechanisms thereby implicating tryptase in both atopic and non-atopic inflammatory conditions. Tryptase can activate proteases such as pro-urokinase and pro-MMP3 (pro-matrix metalloprotease 3, pro-stromelysin), thereby indicating a pathological role in tissue inflammation and remodelling. Furthermore, the recent evidence that tryptase can activate certain G-protein coupled receptors (eg PAR2) and induce neurogenic inflammation points to a broader physiological role, for example in modulating pain mechanisms. Given tryptase's multiple mechanisms of action, it has been proposed that tryptase inhibitors may be beneficial in a broad range of diseases. These include conditions such as: asthma (specifically influencing the inflammatory component, the underlying hyperreactivity, and the chronic fibrotic damage due to smooth muscle thickening); chronic obstructive pulmonary disease (COPD) and pulmonary fibrotic diseases; rhinitis; psoriasis; urticaria; dermatitis; arthritis; Crohn's disease; colitis; angiogenesis; atherosclerosis; multiple sclerosis; interstitial cystitis; migraine headache; neurogenic inflammation and pain mechanisms; wound healing; cirrhosis of the liver; Kimura's disease; pre-eclampsia; bleeding problems associated with menstruation

and the menopause; cancer (particularly melanoma and tumour metastasis); pancreatitis; and certain viral infections (Yong, Exp. Toxic Pathol, 1997, 49, 409; Steinhoff et al., Nat. Med., 2000, 6, 151; Downing and Miyan, Immunol. Today, 2000, 21, 281; Tetlow and Wooley, Ann. Rheum. Dis., 1995, 54, 549; Jeziorska, Salamonsen and Wooley, Biol. Reprod., 1995, 53, 312; Brain, Nat. Med., 2000, 6, 134; Olness et al., Headache, 1999, 39, 101.) The underlying principle is that a tryptase inhibitor should have utility where mast cells have being induced to degranulate by whatever mechanism, including anaphylactic reactions due to exogenous substances, e.g. morphine-induced bronchoconstriction (Bowman and Rand, 2nd edt., 1980.)

It has now been found that certain aromatic compounds carrying lipophilic side chains are particularly effective as inhibitors of serine proteases, especially serine proteases with negatively charged P1 specificity pockets, such as factor Xa, thrombin and tryptase. Depending upon their structure, certain of these compounds have been found to be selective for the serine protease, Factor Xa. Others have been found to be dual inhibitors of Factor Xa and thrombin. Yet others have been found to be selective for the serine protease, tryptase.

The Factor Xa inhibitors of this invention are potentially useful for the prophylaxis or treatment of thrombotic disorders such as amongst others venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, myocardial infarction, and cerebral thrombosis. They potentially have benefit in the treatment of acute vessel closure associated with thrombolytic therapy and restenosis, e.g. after transluminal coronary angioplasty or bypass grafting of the coronary or peripheral arteries

and in the maintenance of vascular access patency in long term hemodialysis patients.

Factor Xa inhibitors of this invention may, with benefit, form part of a combination therapy with an anticoagulant with a different mode of action or with a thrombolytic agent.

Hence, the invention also provides the use of certain compounds which have been found to be inhibitors of both Factor Xa and thrombin. These compounds have excellent potential therapeutic value and may synergistically boost Fxa antithrombotic effect.

It is envisaged that the compounds that are tryptase inhibitors will be useful not only in the treatment and prophylaxis of asthma but also of other allergic and inflammatory conditions mediated by tryptase such as allergic rhinitis, skin conditions such as eczema, psoriasis, atopic dermatitis and urticaria, rheumatoid arthritis, conjunctivitis, inflammatory bowel disease, neurogenic inflammation, atherosclerosis and cancer.

It has been reported in WO99/11658 and WO99/11657 that certain benzamidine and aminoisoquinoline derivatives carrying a bulky lipophilic side chain are excellent inhibitors of serine proteases. Unfortunately, it has since been found that benzamidine compounds of WO 99/11658 in general demonstrate poor oral bioavailability.

Surprisingly, it has now been found that certain other aromatic compounds also show inhibitory activity against serine proteases, in particular Factor Xa, despite the lack of the amidino or 1-aminoisoquinoline functionality previously believed to be crucial for activity as a factor Xa inhibitor, thrombin or tryptase. Many of these compounds also possess structural features in addition to the aromatic

group or properties (such as activity as tryptase inhibitors) that further distinguish them from the compounds of WO99/11658 and WO99/11657.

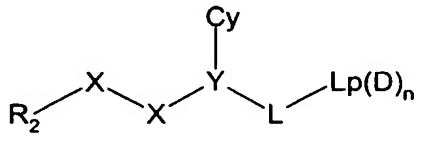
Where compounds of the invention have been tested, they have generally demonstrated superior oral bioavailability in comparison with benzamidines disclosed in WO 99/11658. Also, it has been found that Factor Xa inhibitor compounds of the invention perform excellently in the prothrombin time assay (PT) when compared to aminoisoquinolines of similar Factor Xa activity and structure. The PT assay is a coagulation assay and it is widely accepted that direct acting Factor Xa inhibitors which perform well in the PT assay are more likely to be good antithrombotics.

In WO99/09053 certain 2-aminobenzamide compounds are disclosed as potential motilin receptor antagonists and in US 3268513 similar 2-aminobenzamide compounds are suggested as potential antibacterial agents. However, the novel compounds of the present invention have not before been suggested as potential serine protease inhibitors.

In WO96/09297, WO95/32945, WO94/20527 and US 5,525,623 a variety of peptide based compounds are suggested as potential inhibitors of the mast cell protease tryptase. In WO95/03333 a tryptase inhibitor is provided by a polypeptide obtainable from the leech *hirudo medicinalis*. In WO96/08275 secretory leukocyte protease inhibitor (SLPI) and active fragments thereof have been found to inhibit the proteolytic activity of tryptase. In WO99/55661 certain 4-aminomethylbenzoic ester derivatives are proposed as potential tryptase inhibitors.

Thus viewed from an one aspect the invention provides a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a

condition responsive to a serine protease inhibitor, said method comprising administering to said body an effective amount of a serine protease inhibitor compound of formula (I)



(I)

where R_2 represents a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, hydroxyalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino,

acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

L is an organic linker group containing 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl;

Lp is a lipophilic organic group;

D is a hydrogen bond donor group; and n is 0, 1 or 2; and

R_1, R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a},

or a physiologically tolerable salt thereof, e.g. a halide, phosphate or sulphate salt or a salt with ammonium or an organic amine such as ethylamine or meglumine.

As used herein, the term " treatment" includes prophylaxis, amelioration or elimination of a condition for which a human or non-human animal body is being treated.

The " effective amount" or dosage of the inhibitor compound of formula (I) will depend upon the nature and severity of the condition being treated, the administration route and the size and species of the patient. However in general, quantities of from 0.01 to 100 μmol/kg bodyweight will be administered.

Viewed from a further aspect the invention provides the use of a serine protease inhibitor compound of formula I as defined hereinabove, or physiologically tolerable salt thereof, for the manufacture of a medicament for use in a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat (i.e. treat or prevent) a condition responsive to said inhibitor.

The serine protease is preferably a serine protease with a negatively charged P1 specificity pocket (i.e. trypsin-like).

It has further been found that compounds of formula (I) in which R_1 is an unsubstituted aminoalkyl group, are selective inhibitors of tryptase. Compounds of formula (I) in which R_1 represents other than an unsubstituted aminoalkyl group have been found to be selective inhibitors of Factor Xa, or selective dual inhibitors of Factor Xa and thrombin.

According to another aspect, therefore, the present invention provides a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a condition responsive to a Factor Xa inhibitor (e.g. a condition such as a thrombotic disorder, including venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, myocardial infarction and cerebral thrombosis, acute vessel closure associated with thrombolytic therapy and restenosis, including after transluminal coronary angioplasty or bypass grafting of the coronary or peripheral arteries and in the maintenance of vascular access patency in long term hemodialysis patients), said method comprising administering to said body an effective amount of a serine protease inhibitor compound of formula (I) as defined hereinabove, provided that R_1 is not

an unsubstituted aminoalkyl group, or a physiologically tolerable salt thereof.

According to another aspect, therefore, the present invention provides a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a condition responsive to a tryptase inhibitor (e.g. a condition such as asthma, allergic rhinitis, eczema, psoriasis, atopic dermatitis, urticaria, rheumatoid arthritis, conjunctivitis, inflammatory bowel disease, neurogenic inflammation, atherosclerosis or cancer), said method comprising administering to said body an effective amount of a serine protease inhibitor compound of formula (I) as defined hereinabove which is substituted in the 3 and/or 4 position by R_1 and in which R_1 is an unsubstituted aminoalkyl group, or a physiologically tolerable salt thereof.

The present invention further provides the use of a serine protease inhibitor compound of formula (I) as defined hereinabove, provided that R_1 is not an unsubstituted aminoalkyl group, or a physiologically tolerable salt thereof for the manufacture of a medicament for use as a Factor Xa inhibitor.

The present invention further provides the use of a serine protease inhibitor compound of formula (I) as defined hereinabove, which is substituted in the 3 and/or 4 position by R_1 and in which R_1 is an unsubstituted aminoalkyl group, or a physiologically tolerable salt thereof for the manufacture of a medicament for use as a tryptase inhibitor.

In the compounds of formula (I), where the alpha atom is carbon it preferably has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X.

Likewise the fourth substituent R_{1b} at an alpha carbon is preferably a methyl or hydroxymethyl group or hydrogen.

In the compounds of formula (I), unless otherwise indicated, aryl groups preferably contain 5 to 10 ring atoms optionally including 1, 2 or 3 heteroatoms selected from O, N and S; alkyl, alkenyl or alkynyl groups or alkylene moieties preferably contain up to 6 carbons, e.g. C_{1-6} or C_{1-3}; cyclic groups preferably have ring sizes of 3 to 8 atoms; and fused multicyclic groups preferably contain 8 to 16 ring atoms.

Examples of particular values for R_{1a} are: hydrogen, methyl or ethyl. R_{1a} is preferably a hydrogen atom.

The linker group from the R_2 group to the alpha atom is preferably selected from -CH=CH-, -CONH-, -CONR$_{1a}$-, -NH-CO-, -NH-CH_2-, -CH_2-NH-, -CH_2O-, -OCH_2-, -COO-, -OC=O- and -CH_2CH_2-. Preferably, the X moiety nearest to the alpha atom is an NH or O atom, most preferably a NH group. The X moiety alpha to the aromatic ring is preferably a carbon based group such as CH_2 or CO, preferably CO. Thus a particularly preferred linker X-X is -CONH-. In an alternative embodiment the linker is preferably a -OCH_2- group.

Examples of particular values for R_{1b} are: hydrogen, (1-4C)alkyl, such as methyl or hydroxy(1-4C)alkyl, such as hydroxymethyl. R_{1b} is preferably a hydrogen atom.

The alpha atom (Y) is preferably a CH or C(CH_3) group, especially CH.

The linker group from the alpha atom to the lipophilic group is preferably CO, CH_2NH, $CONR_{1d}(CH_2)_m$, $(CH_2)_mN(R_{1d})CO(CH_2)_m$, $(CH_2)_{m+2}$, $CO(CH_2)_m$, $(CH_2)_mCO$, $(CH_2)_mOC=O$, $(CH_2)_mO$, $CH=CH(CH_2)_m$, SO_2, SO_2NR_{1d}, $SO_2(CH_2)_m$,

$(CH_2)_mSO_2$ or $(CH_2)_mSO_2NR_{1d}$ (where each m is independently 0 or 1 and R_{1d} is as defined for R_{1a}).

Examples of particular values for R_{1d} are: hydrogen; for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkyl, such as methyl or ethyl, or aryl(1-6C)alkyl, such as benzyl or phenylethyl; for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (2-6C)carboxamido, such as carboxamidomethyl; for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)carboxyalkyl, such as carboxymethyl, carboxyethyl or carboxypropyl; for alkoxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-5C)alkoxycarbonyl(1-6C)alkyl, such as methoxycarbonylmethyl, methoxycarbonylethyl, methoxycarbonylpropyl, ethoxycarbonylmethyl, ethoxycarbonylethyl and ethoxycarbonylpropyl.

R_{1d} is preferably a hydrogen atom.

The linker may be optionally branched, for example, to incorporate a polar functionality.

Examples of particular values for L are CO, CONH, CH_2NHCO and $CONHCH_2$.

It will be appreciated by those skilled in the art that a diverse range of organic groups are lipophilic, and that it is therefore impractical to define with precision each and every structure that may be incorporated into a serine protease inhibitor compound of formula (I). Accordingly, it is being assumed that the addressee of this specification will not require an exhaustive computer listing of structures of lipophilic groups, but will instead make use

of the structures of lipophilic groups disclosed in the specification, especially those exemplified; the test systems described herein for identifying serine protease inhibitors; and common general knowledge of the lipophilicity, synthesis and stability of organic compounds, to obtain novel serine protease inhibitor compounds of formula (I).

The lipophilic group may be, for example, an alkyl, alkenyl, carbocyclic or heterocyclic group, or a combination of two or more such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO_2, $CONR_{1e}$, NR_{1e}-CO-, NR_{1e} linkage (where R_{1e} is as defined for R_{1a}), optionally substituted by one or more oxo or R_3 groups in which R_3 is alkylaminocarbonyl, alkoxycarbonylamino, N-alkylaminoalkanoyl, N-alkanoylaminoalkanoyl, C-hydroxyaminoalkanoyl or as defined for R_{3a}.

By way of illustration, representative lipophilic groups include methylcyclohexyl, methylcyclohexylmethyl, methylphenylmethyl, phenylethyl, benzylpiperidinyl, benzoylpiperidinyl, bispiperidinyl and phenylpiperazinyl.

Phenylethyl is an example of a combination of an alkyl group and a carbocyclic group linked through a single bond.

Benzylpiperidinyl is an example of a combination of an alkyl group, a carbocyclic group and a heterocyclic group linked by single bonds.

Benzoylpiperidinyl is an example of a combination of a carbocyclic group and a heterocyclic group linked through C=O.

Methylcyclohexylmethyl is an example of a combination of an alkyl group (methyl) and a carbocyclic group (cyclohexyl) linked by a single bond and having a substituent R_3 (methyl) on cyclohexyl. It will be

appreciated that this group could alternatively have been regarded as a combination of two alkyl groups and a carbocyclic group. However, in order to provide clarity, in this specification any terminal alkyl group in Lp will be treated as a substituent R_3.

When the lipophilic group comprises an alkyl group, this may be, for example, a (1-3C) alkyl group, such as methyl, ethyl or propyl. Preferably an alkyl group is unsubstituted.

When the lipophilic group comprises a carbocyclic group, this may be, for example, a non-aromatic or aromatic, mono or polycyclic hydrocarbon group containing up to 25, more preferably up to 10 carbon atoms. The carbocyclic group may thus be, for example, a cycloalkyl, polycycloalkyl, phenyl or naphthyl group, or a cycloalkyl group fused with a phenyl group.

Examples of particular values for a cycloalkyl group are (3-6C) cycloalkyl groups, such as cyclopentyl and cyclohexyl. A cycloalkyl group is preferably unsubstituted or substituted by one group R_3, preferably amino or an alkyl group, such as methyl.

Examples of particular values for a polycycloalkyl group are (6-10C) polycycloalkyl groups, such as bicycloalkyl, for example decalinyl, norbornyl or adamantyl. A polycycloalkyl group is preferably unsubstituted or substituted by one, two or three R_3 groups, for example alkyl such as methyl. An example of a polycycloalkyl group substituted by alkyl is isopinocamphenyl.

A phenyl group is preferably unsubstituted or substituted by one or two R_3 groups. More preferably it is substituted by one or two R_3 groups.

A naphthyl group is preferably unsubstituted or substituted by one R_3 group.

Examples of a cycloalkyl or cycloalkenyl group fused with a phenyl group are indanyl and tetrahydronaphthyl. This group is preferably unsubstituted or substituted by oxo or one or two R_3 groups. Examples of groups substituted by oxo are 1-oxoindan-5-yl, 1-oxo-5,6,7,8-tetrahydronaphth-5-yl and 1-oxo-5,6,7,8-tetrahydronaphth-6-yl.

When the lipophilic group comprises a heterocyclic group, this may be, for example, a non-aromatic or aromatic, mono or polycyclic group containing one or two oxygen, nitrogen or sulfur atoms in the ring system, and in total up to 25, more preferably up to 10 ring system atoms.

Examples of a heterocyclic group when it is a non-aromatic monocyclic group are azacycloalkyl groups, such as pyrrolidinyl and piperidinyl; azacycloalkenyl groups, such as pyrrolinyl; diazacycloalkyl groups, such as piperazinyl; oxacycloalkyl groups, such as tetrahydropyranyl; and thiacycloalkyl groups, such as tetrahydrothiopyranyl. A non-aromatic monocyclic group preferably contains 5, 6 or 7 ring atoms and is preferably unsubstituted or substituted by one group R_3, preferably alkyl, such as methyl or ethyl, or hydroxyalkyl, such as hydroxymethyl.

Examples of a heterocyclic group when it is a non-aromatic polycyclic group are bicyclic groups, such as azacycloalkyl fused with phenyl, for example dihydroindolyl, dihydroisoindolyl, tetrahydroquinolinyl and tetrahydroisoquinolinyl; azacycloalkyl fused with cycloalkyl, such as decahydroisoquinolyl, and tricyclic groups, such as azacycloalkyl fused with indolyl, for example tetrahydropyrido[3,4-b]indole. This group is preferably unsubstituted.

Examples of a heterocyclic group when it is an aromatic monocyclic group are furyl, pyrrolyl, thienyl, imidazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, oxadiazolyl (such as 1,3,4-oxadiazolyl), thiadiazolyl (such as 1,3,4-thiadiazolyl), triazinyl and thiazolyl. This group is preferably unsubstituted or substituted by one or two R_3 groups.

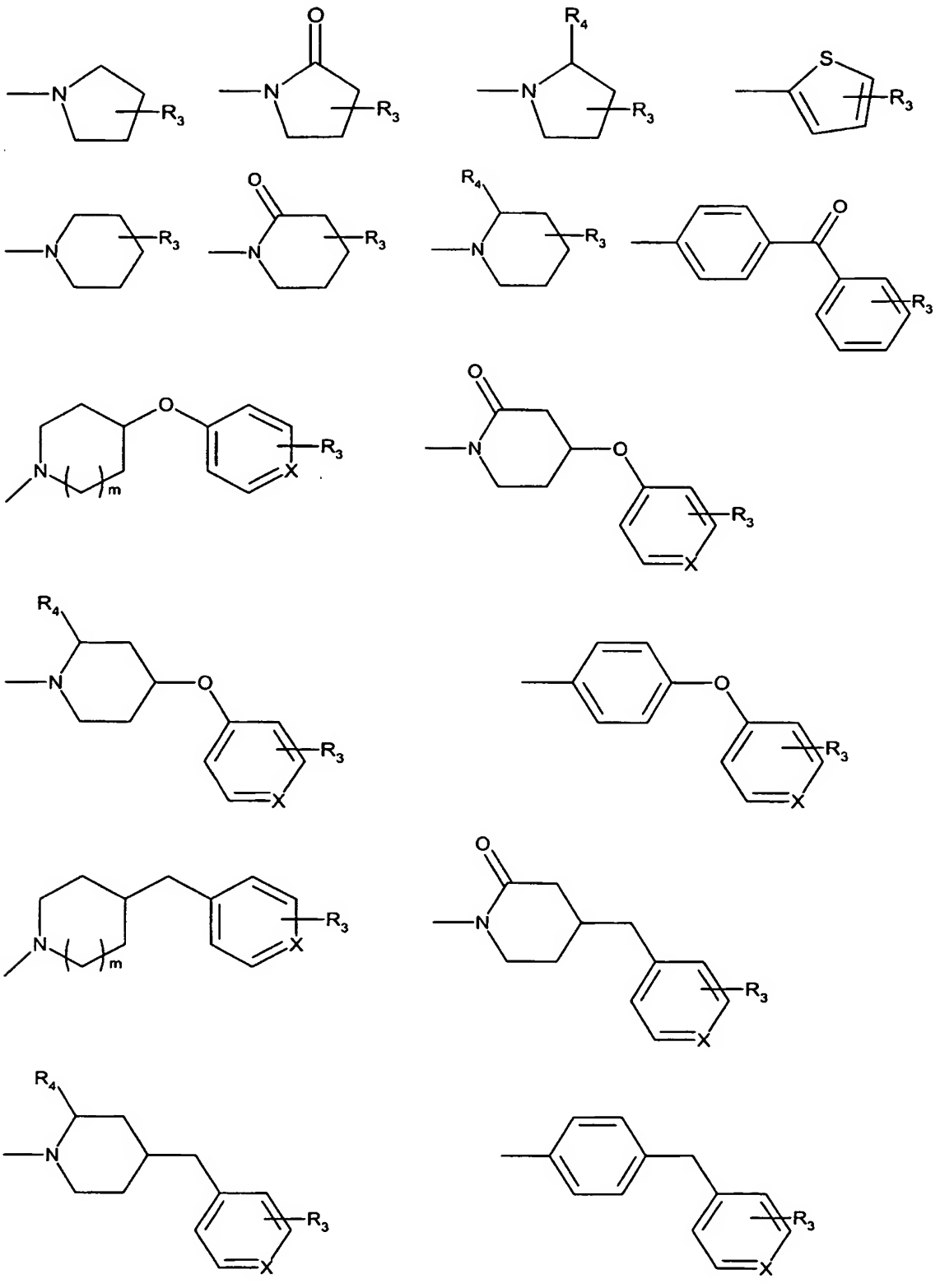
Examples of a heterocyclic group when it is an aromatic polycyclic group are bicyclic groups such as benzofuryl, quinolinyl, isoquinolinyl, benzothienyl, indolyl and benzothiazolyl. This group is preferably unsubstituted or substituted by one R_3.

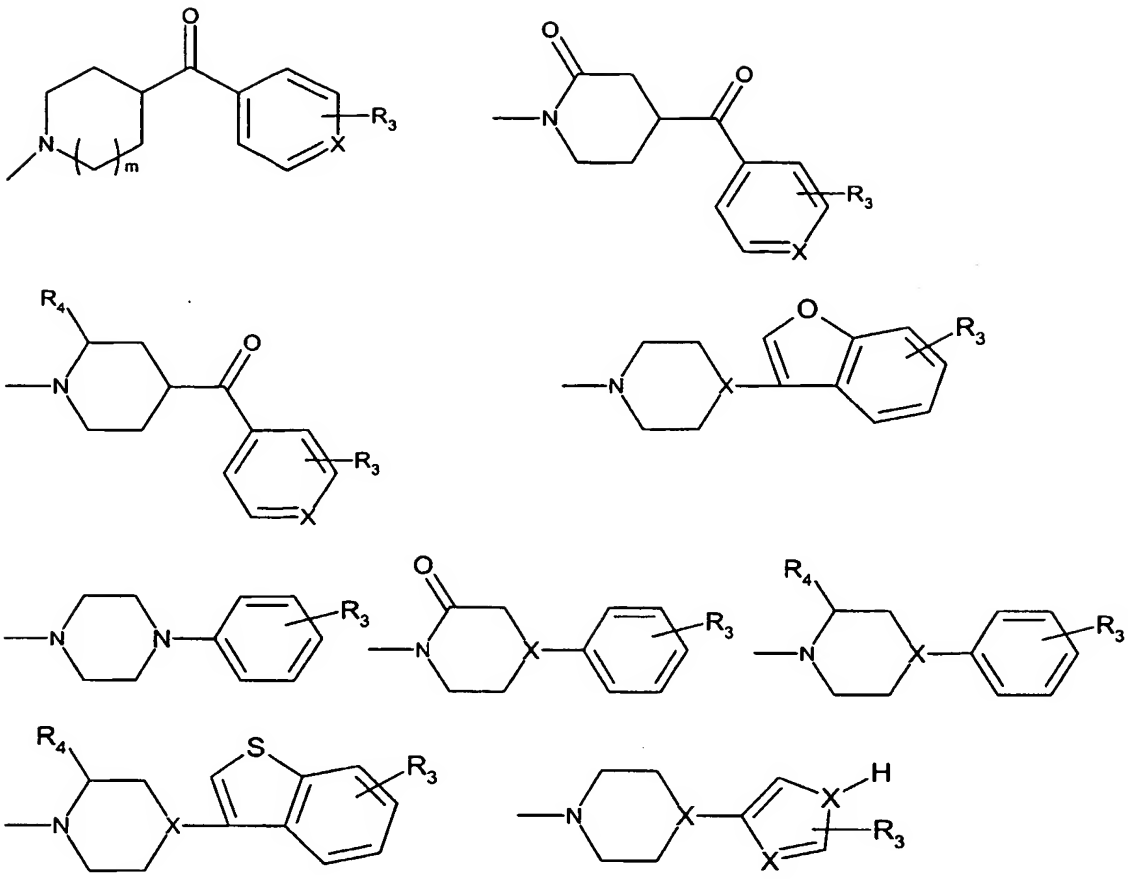
The lipophilic group preferably comprises a cycloalkyl, azacycloalkyl, diazacycloalkyl, phenyl, naphthyl, adamantyl, bicycloalkyl, mono- or diazabicycloalkyl, mono- or bicyclo heteroaromatic or a linear or branched alkyl or alkenyl group all optionally substituted by one or more oxo or groups R_3, or a combination of at least two such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO_2, $CONR_{1e}$, NR_{1e}-CO- or NR_{1e} linkage (where R_{1e} is as defined for R_{1a}).

Where Lp comprises a combination of at least two groups, it preferably comprises a combination of two or three such groups. The groups are preferably linked by a single bond, C=O, O or NR_{1e}.

Examples of particular values for R_{1e} are hydrogen and (1-6C)alkyl, such as methyl or ethyl.

The lipophilic group Lp may be selected, for example, from:





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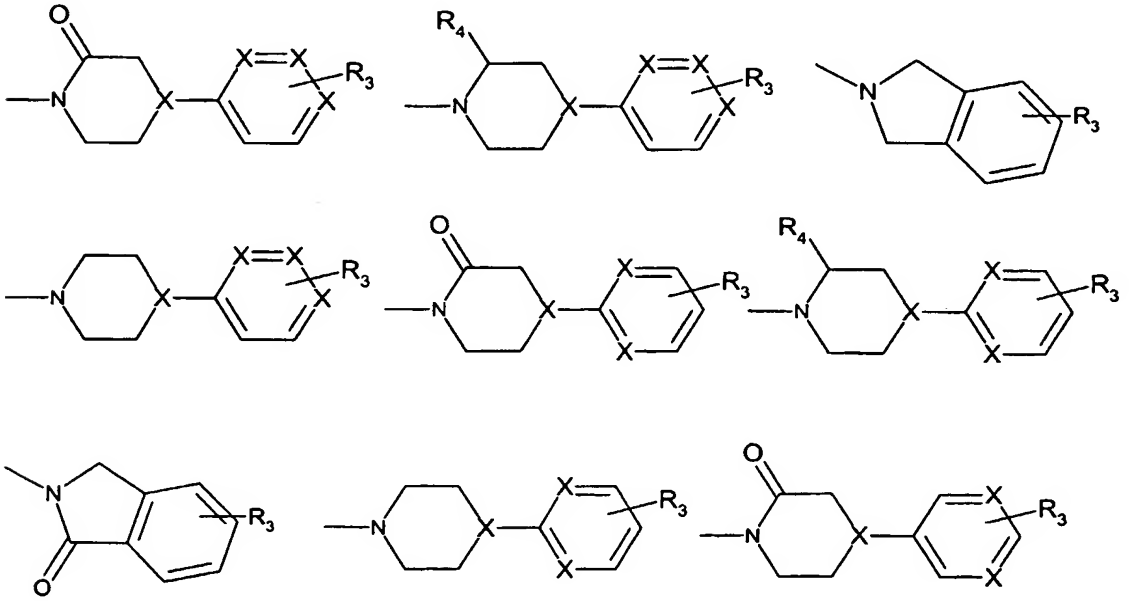
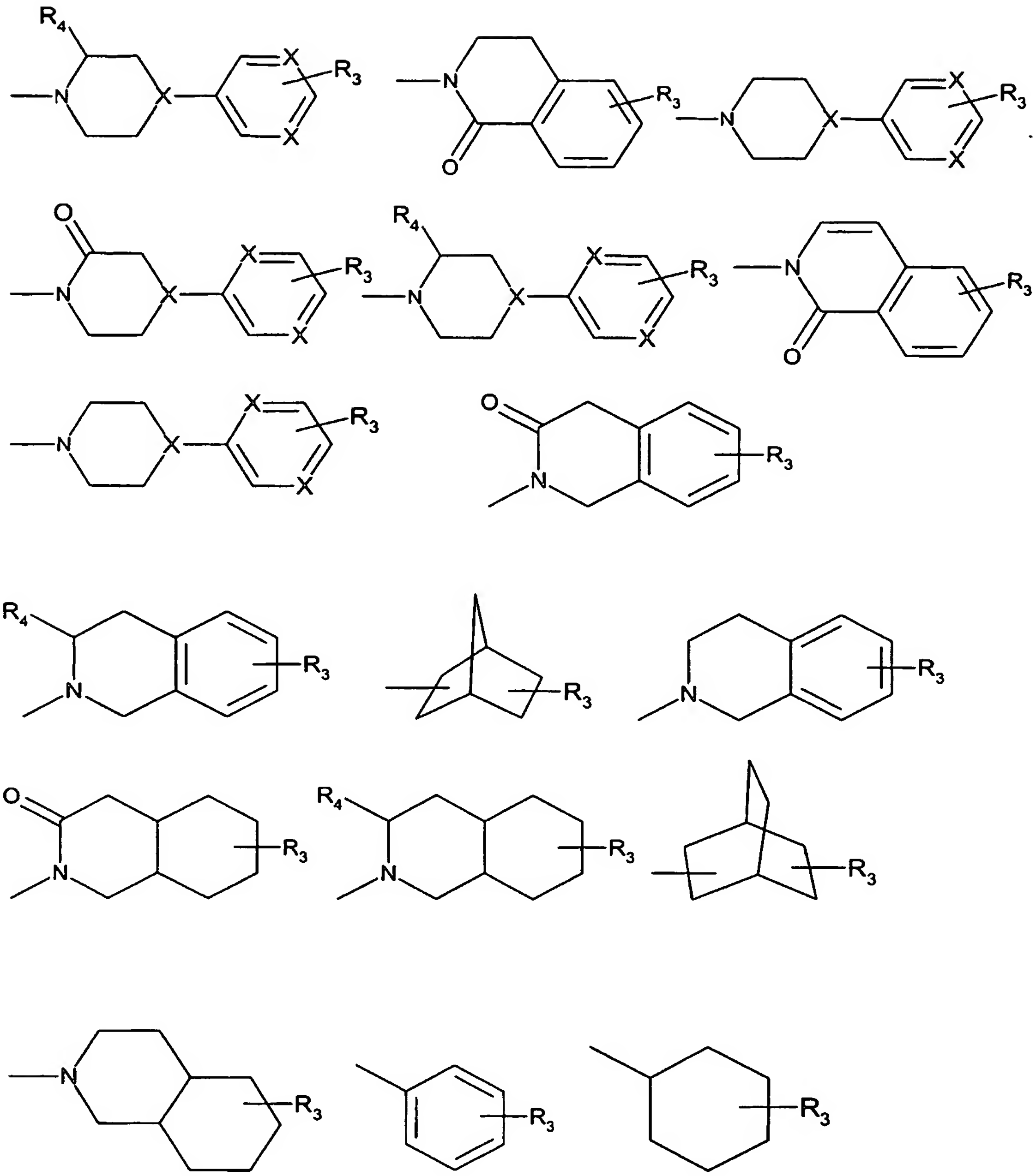
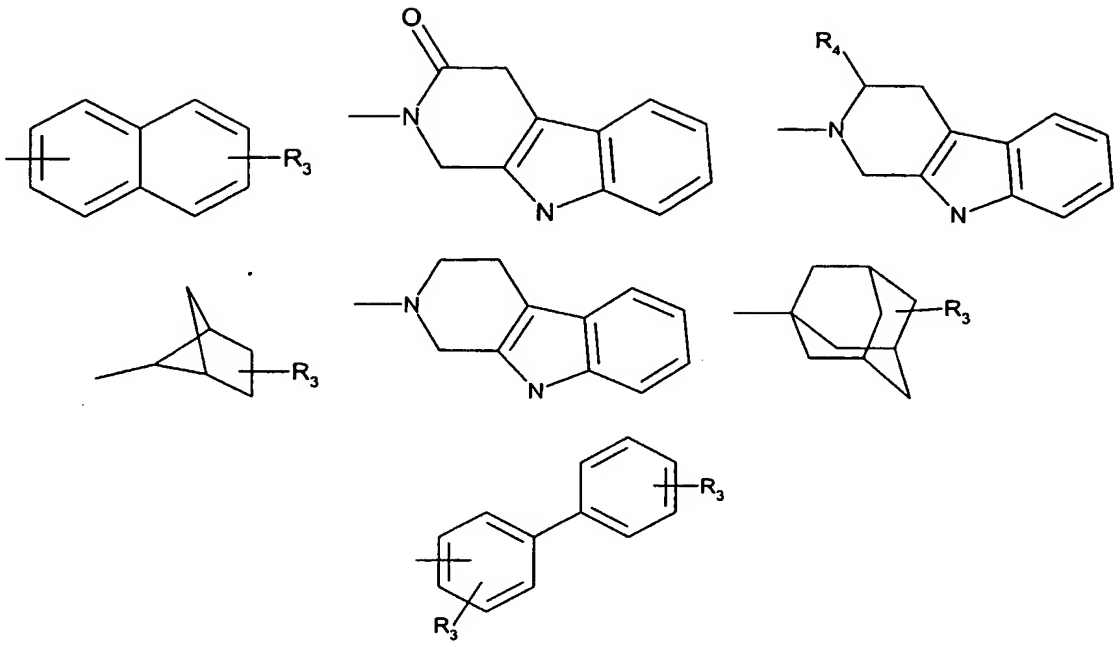



R4
R3
X
N
O
R4
R3
N
O
R3
R4
R3
N
O
R3



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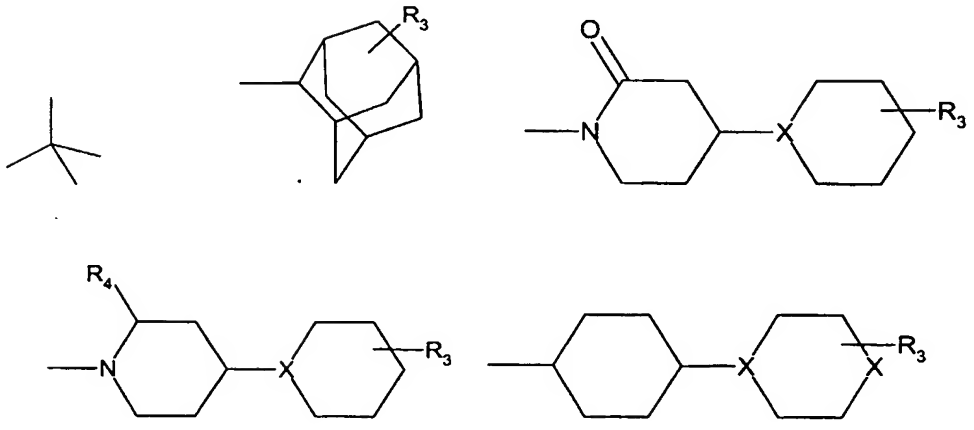

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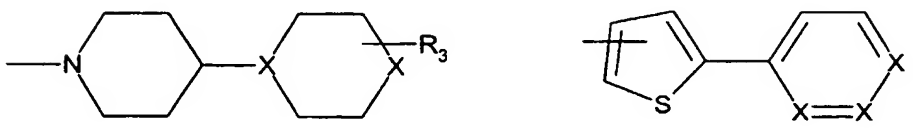

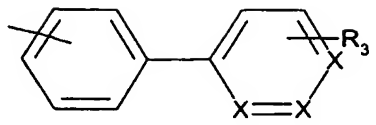

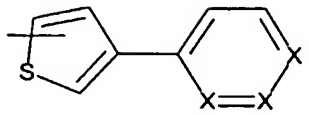

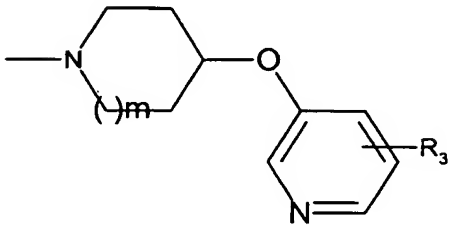

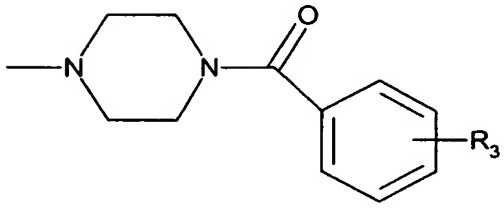

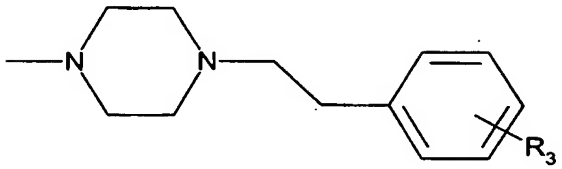

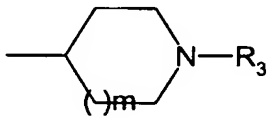

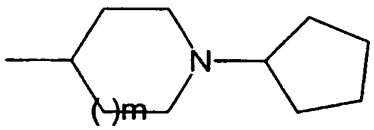

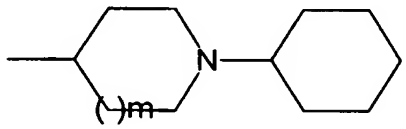

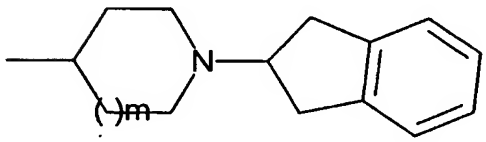

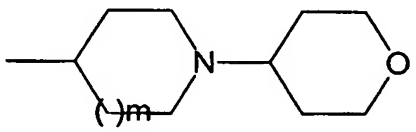

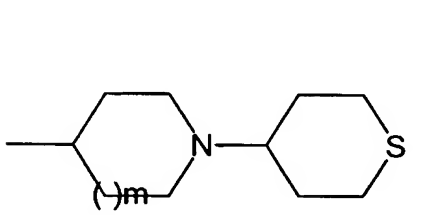

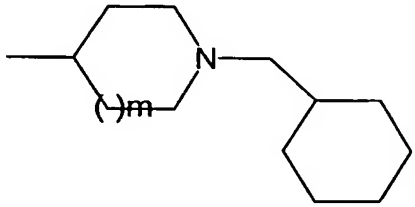

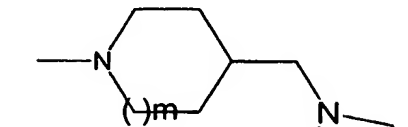

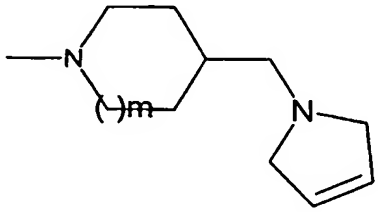

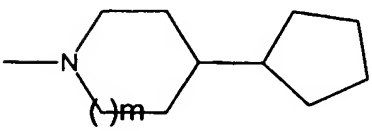

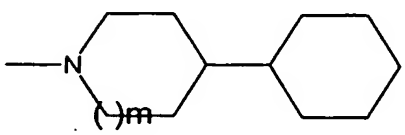

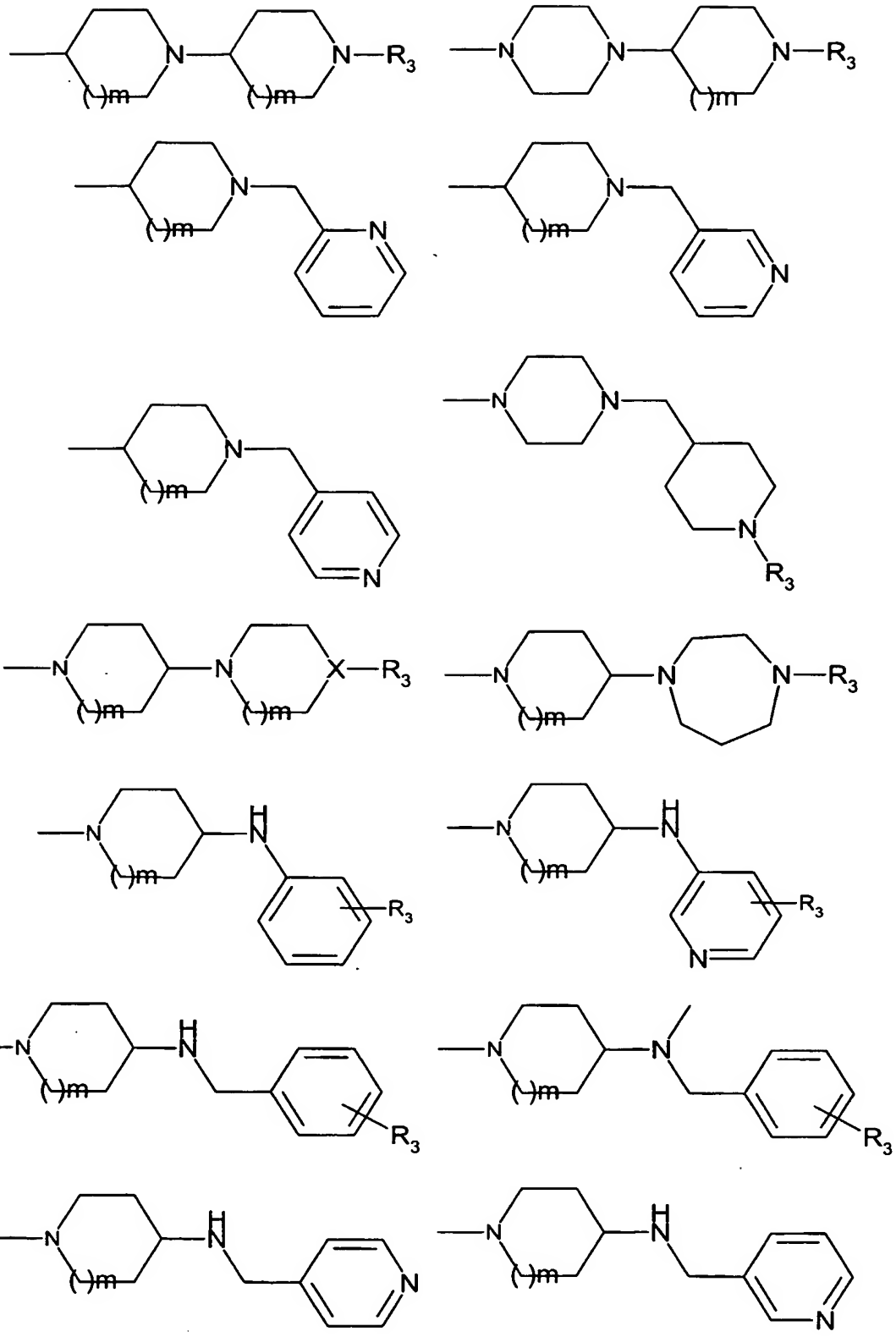

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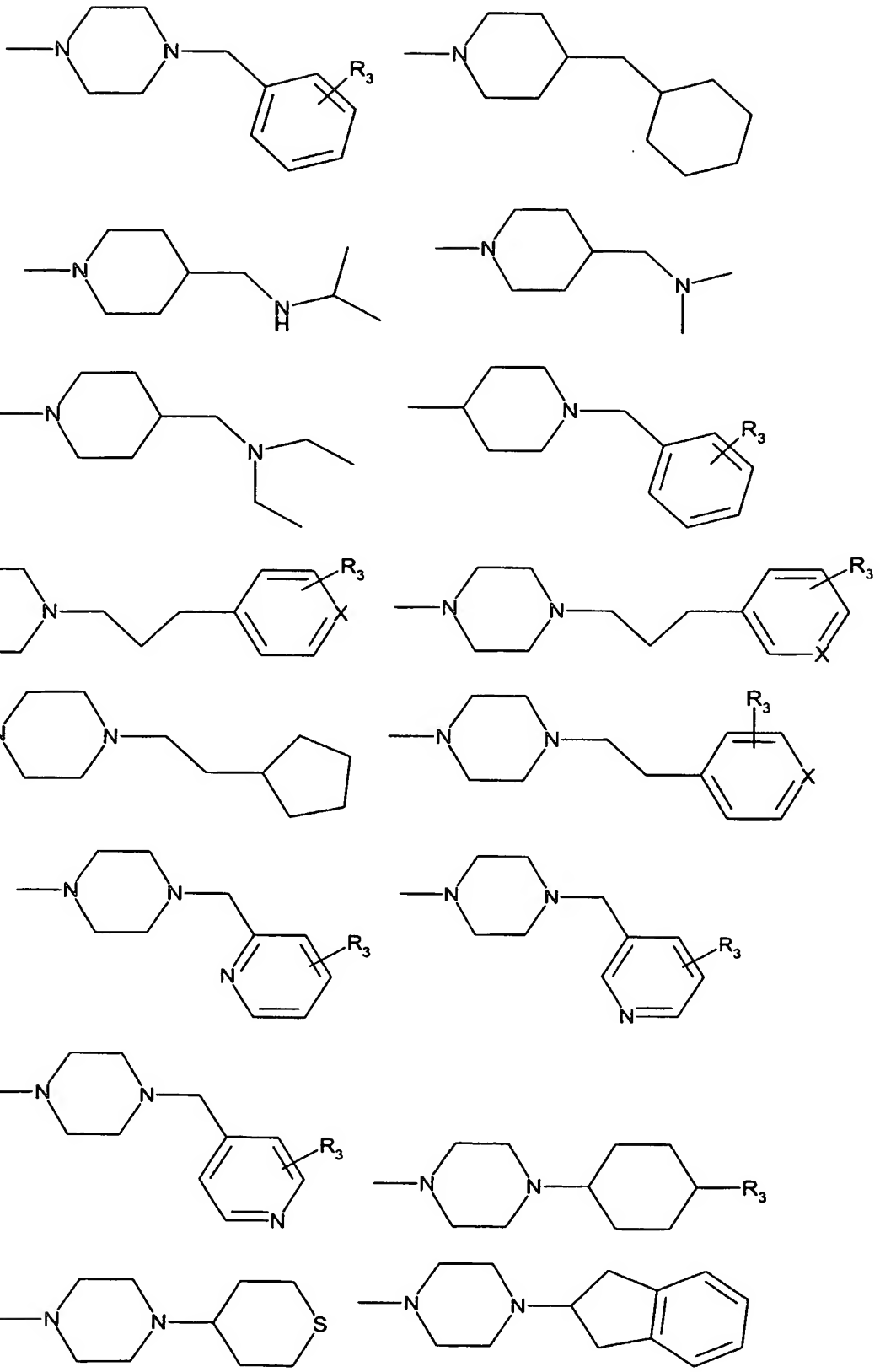
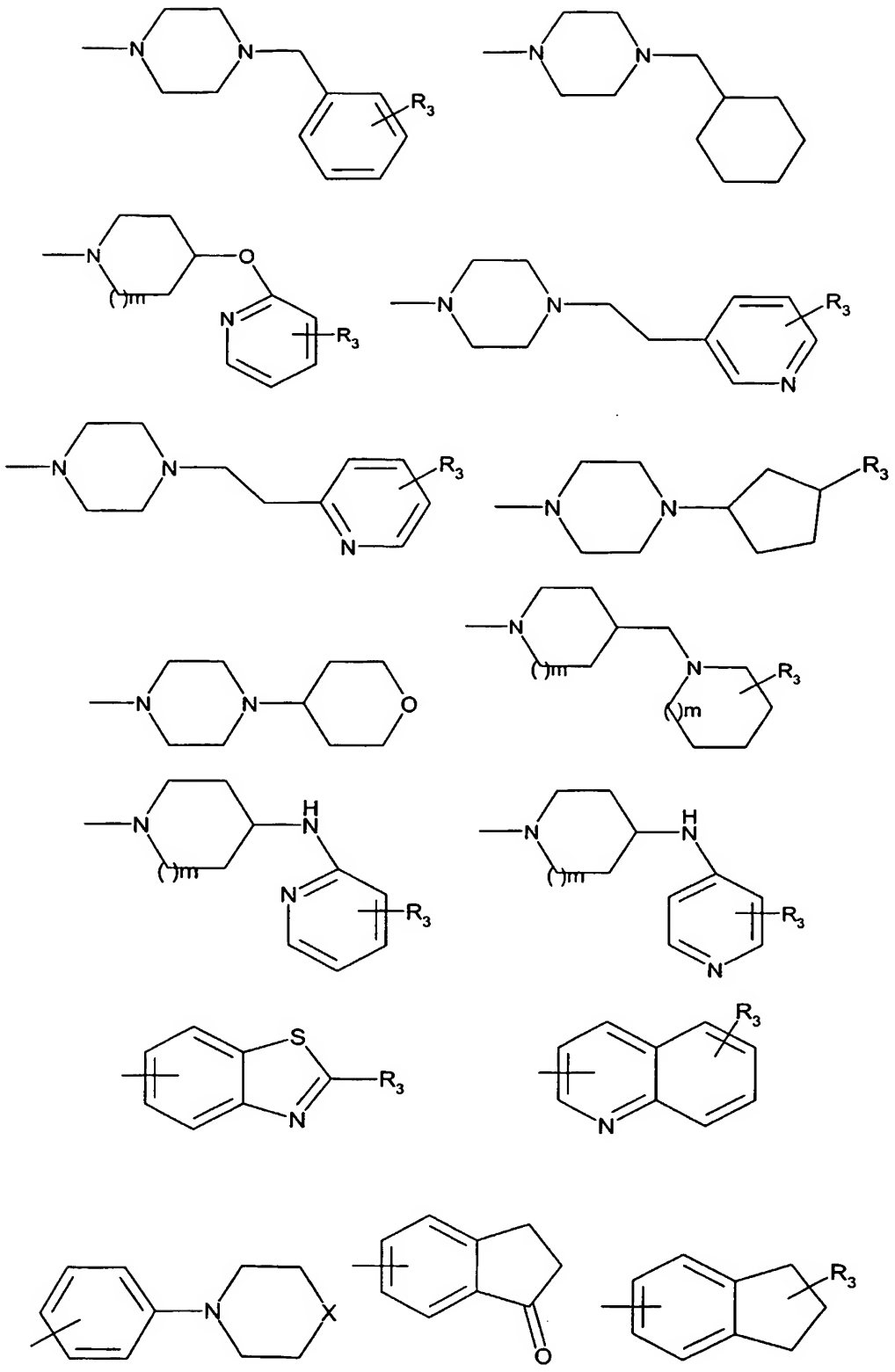
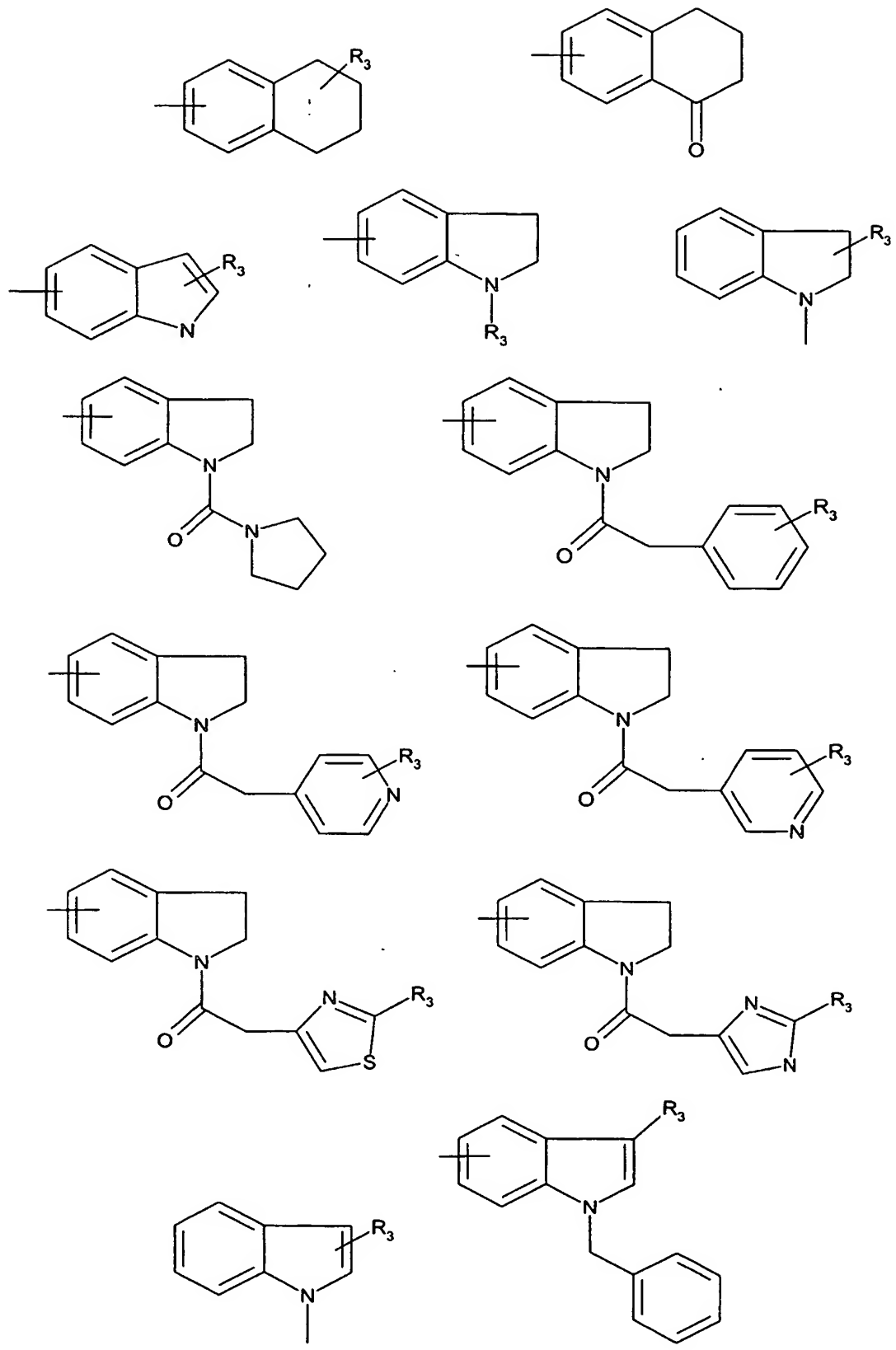






wherein R_3 is as hereinbefore defined;

m represents 0 or 1;

R_4 represents hydrogen, $(CH_2)_wCOOH$ or $(CH_2)_wCONH_2$;

w represents an integer from 0 to 4; and

X represents CH or N.

Where two or more X atoms are present in a ring, preferably at least one is CH.

In the Lp groups depicted above, preferably L represents CO when the Lp group is linked to L through N, or CONH when the Lp group is linked to L through C.

Examples of particular values for R_3 are:-

for alkylaminocarbonyl: N-methyl-N-ethylaminocarbonyl, methylaminocarbonyl or dimethylaminocarbonyl;

for N-alkylaminoalkanoyl: N-methylacetyl;

for N-alkanoylaminoalkanoyl: 2-N-acetylaminoacetyl or 2-N-acetylaminopropanoyl;

for C-hydroxyaminoalkanoyl: 2-amino-3-hydroxypropanoyl or 2-amino-3-hydroxybutanoyl;

hydrogen;

hydroxyl;

for alkoxy optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkoxy such as methoxy or ethoxy;

for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkyl, such as methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, t-butyl, pentyl, 2-pentyl or 3-pentyl, (1-6C)alkylamino(1-6C)alkyl, such as isopropylaminomethyl, dimethylamino-methyl, diethylaminomethyl or dimethylaminoethyl, or (1-6C)alkanoyl, such as acetyl, propionyl or isobutyryl;

for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)hydroxyalkyl, such as hydroxymethyl, or 1-hydroxyethyl or 2-hydroxyethyl, carboxy, carboxy(1-5C)alkyl or hydroxy(1-6C)alkanoyl, such as 2-hydroxyacetyl or 2-hydroxypropanoyl;
for alkoxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkoxy(1-6C)alkyl, such as methoxymethyl;
for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl:
for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: amino(1-6C)alkyl such as aminomethyl, aminocarbonyl, aminocarbonyl-(1-5C)alkyl, or amino(1-6C)alkanoyl, such as aminoacetyl ($COCH_2NH_2$), aminopropionyl ($COCH_2CH_2NH_2$) or 2-aminopropionyl ($COCH(CH_3)NH_2$);
for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkylamino such as methylamino, dimethylamino or ethylamino, or (1-6C)alkanoylamino, such as formylamino or acetylamino;
amino;
for halo: fluoro or chloro;
cyano;
nitro;
thiol;
for alkylthio: methylthio;
for alkylsulphonyl: methylsulphonyl, ethylsulphonyl or isopropylsulphonyl;
for alkylsulphenyl: methylsulphenyl;
for triazolyl: 1,2,4-triazol-2-yl, 1,2,4-triazol-4-yl or 1,2,3-triazol-4-yl;
for imidazolyl: 1,3-imidazol-1-yl or 1,3-imidazol-4-yl;

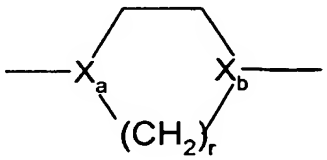
for tetrazolyl: tetrazol-1-yl or tetrazol-5-yl;
hydrazido;
for alkylsulphonamido: methylsulphonamido, ethylsulphonamido or propylsulphonamido;
for alkylaminosulphonyl: methylaminosulphonyl, ethylaminosulphonyl or propylaminosulphonyl;
aminosulphonyl;
for haloalkoxy: trifluoromethoxy; and
for haloalkyl: trifluoromethyl or trichloromethyl.

When R_3 is present as a substituent on an aromatic ring, it may be selected, for example, from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

When R_3 is present as a substituent on a saturated ring, it may be selected, for example, from hydrogen, hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl and ethoxycarbonyl.

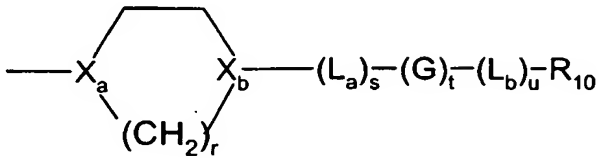
It has been found that certain groups L and, especially, Lp are associated with selectivity for Factor Xa, whereas others are associated with selectivity for tryptase.

One group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which Lp comprises an azacycloalkyl or diazacycloalkyl group of formula



in which r is 1 or 2, one of X_a and X_b is N and the other is CH or N, provided that when r is 1, X_a and X_b are not both N.

Preferred compounds comprising this group are those in which Lp is a group of formula:



in which:

r is 1 or 2;

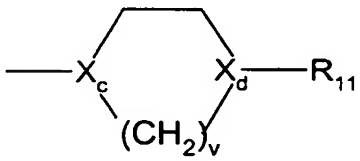
one of X_a and X_b is N and the other is CH or N provided that when r is 1, X_a and X_b are not both N;

s, t and u are each 0 or 1;

L_a and L_b are each independently selected from a single bond, C=O, O and NR_{1e}, in which R_{1e} is hydrogen or (1-6C)alkyl;

G is (1-6C)alkanediyl; and

R_{10} is (1-6C)alkyl; (3-6C)cycloalkyl which is unsubstituted or substituted by (1-6C)alkyl; indanyl; pyridyl; tetrahydropyranyl; tetrahydrothiopyranyl; phenyl which is unsubstituted or substituted by one or two R_3 groups; pyrrolinyl; or a group of formula



in which v is 1, 2 or 3; one of X_c and X_d is N and the other is CH or N, provided that when v is 1, X_c and X_d are not both N; and R_{11} is hydrogen, (1-6C)alkyl or when X_d is CH, hydroxy(1-6C)alkyl; provided that when t is 0, the sum of s and u is 1; when X_b is N, L_a is a bond or C=O; when X_c is N, L_b is a bond or C=O; when X_b and X_c are both N, t is 1; and

when $(L_a)_s$-$(G)_t$-(L_b) represents an alkyl group and X_b and X_c both represent N, the alkyl group contains at least two chain carbon atoms.

It will be appreciated that the provisos exclude compounds having two heteroatoms bonded directly together or separated by an alkyl group having only one carbon atom in the chain.

When X_a is N, L is preferably CO or CH_2CO.

When X_a is CH, L is preferably CONH, $CONHCH_2$ or CH_2NHCO.

Examples of values for G are CH_2, $(CH_2)_2$ and $(CH_2)_3$.

Examples of values for R_{11} are hydrogen, methyl, ethyl or 2-propyl, or when X_d is CH, hydroxymethyl.

Examples of values for R_{10} are:

for (1-6C)alkyl: methyl, ethyl, 2-propyl and 3-pentyl;

for (3-6C)cycloalkyl which is unsubstituted or substituted by (1-6C)alkyl: cyclopentyl, 3-methylcyclopentyl, cyclohexyl and 4-methylcyclohexyl;

for indanyl: 2-indanyl;

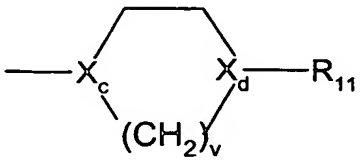
for pyridyl: pyrid-2-yl, pyrid-3-yl and pyrid-4-yl;

for tetrahydropyranyl: tetrahydropyran-4-yl;

for tetrahydrothiopyranyl: tetrahydrothiopyran-4-yl;

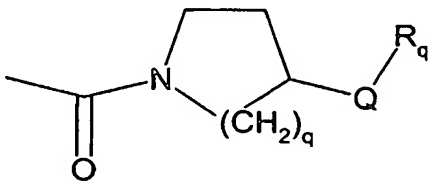
for phenyl which is unsubstituted or substituted by one or two R_3 groups: phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-(methylthio)phenyl, 2-ethylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methanesulphonylphenyl, 3-methanesulphonylphenyl, 4-methanesulphonylphenyl, 4-fluoro-2-methanesulphonylphenyl, 4-amino-2-methanesulphonylphenyl, 4-amido-2-methanesulphonyl-phenyl, 4-nitro-2-methanesulphonylphenyl, 2-aminosulphonylphenyl, 2-methylaminosulphonylphenyl, 2-

dimethylaminosulphonylphenyl, 2-methylsulphonylamino-phenyl, 2-carboxamidophenyl and 2-acetamidophenyl;
for pyrrolinyl: pyrrolin-1-yl; and
for a group of formula



piperidin-1-yl, 4-methyl-piperidin-1-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-(2-propyl)piperidin-4-yl, pyrrolidin-1-yl, 3-methylpyrrolidin-1-yl, pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-(2-propyl)pyrrolidin-3-yl, 1-methyl-piperazin-4-yl, 1-ethylpiperazin-4-yl, 1-(2-propyl)piperazin-4-yl, hexahydro-1,4-diazapin-1-yl and 4-methyl-hexahydro-1,4-diazapin-1-yl.

Another group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which -L-Lp(D)$_n$ is



q is 1 or 2;

(a) Q is a direct bond; and R_q is piperidin-4-yl which may bear a C_{1-3}alkyl substituent at the 1-position; or R_q is NR_aR_b in which each of R_a and R_b independently is hydrogen or C_{1-3}alkyl; or one of R_a and R_b is hydrogen or methyl and the other of R_a and R_b is $-CH_2-R_c$ or $-CH_2-R_d$ in which R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which R_d is isopropyl or

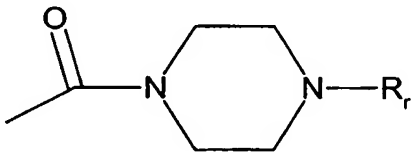
cyclopentyl, or NR_aR_b is pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino may be a 3,4-didehydro deriviative and in which a pyrrolidino, piperidino, piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position (preferably R_q is piperidin-4-yl which may bear a (1-3C)alkyl substituent at the 1-position);

(b) Q is -O- or -NH-; and R_q is R_c which is defined as above (R_c is preferably pyrid-2-yl, pyrid-3-yl or pyrid-4-yl); or

(c) Q is methylene; and R_q is NR_aR_b which is defined as above.

q is preferably 2.

Another group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which $-L-Lp(D)_n$ is

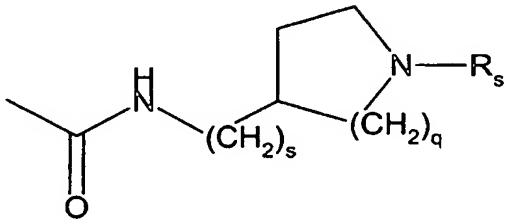


in which R_r is $-(CH_2)_c-R_c$, $-CHR_eR_f$, $-CH_2-CHR_eR_f$, or R_g in which c is 1 or 2 and R_c is defined as above; each of R_e and R_f independently is hydrogen or C_{1-3}alkyl; or CHR_eR_f is cyclopentyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), cyclohexyl(which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a 1-methyl substituent), piperidin-4-yl (which may bear a 1-methyl substituent), or indan-2-yl; and R_g is 2-methylsulphonylphenyl which may bear a 4-fluoro substituent or R_g is λ^6-1,1-dioxobenzo[b]thiophen-7-yl.

Preferably c is 2.

Preferably R_c is pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

Another group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which -L-Lp(D)$_n$ is



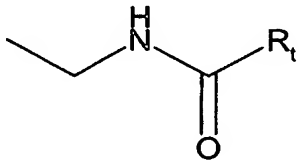
in which q is 1 or 2;

s is 0 or 1; and

R_s is $-(CH_2)_c-R_c$, $-CHR_eR_f$, or $-CH_2-CHR_eR_f$ each of which is defined as above.

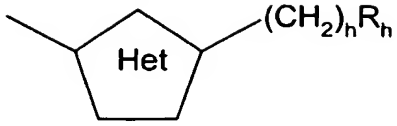
Preferably s is 1.

Another group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which -L-Lp(D)$_n$ is



in which R_t is piperidin-4-yl, piperidin-3-yl or pyrrolidin-3-yl (especially piperidin-4-yl), any of which may bear a C_{1-3} alkyl substituent at the 1-position (preferably methyl, ethyl or, more preferably, 2-propyl); or R_t is phenyl (which phenyl may bear a fluoro, chloro, C_{1-4} alkyl, methoxy or methylsulphonyl substituent).

Another group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which -L-Lp(D)$_n$ is

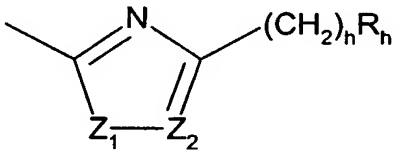


in which Het is a divalent 5 membered heteroaromatic group containing 1, 2 or 3 heteroatoms selected from O, N and S and having the two ring atoms at which it is connected separated by one ring atom;

h is 0 or 1; and

R_h is phenyl which may bear one or more R_3 substituents, for example independently selected from, for an ortho or a para substituent: C_{1-5} alkyl, fluoro, chloro, difluoromethyl, trifluoromethyl, methoxy, dimethylamino, methylsulphonyl, and C_{1-2} acyl, and for a meta substituent: fluoro, chloro and methyl.

Within this sub-group, a particularly preferred group of compounds is that in which -L-Lp(D)$_n$ is

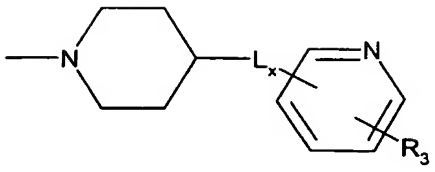


in which R_h is phenyl which may bear one or two R_3 substituents, for example an ortho and/or a para substituent independently selected from, for an ortho: methyl, fluoro, chloro, methylsulphonyl and acetyl, and for a para substituent: methyl, fluoro, chloro, methoxy and dimethylamino;

Z_1 is S, Z_2 is CH, h is 0; or

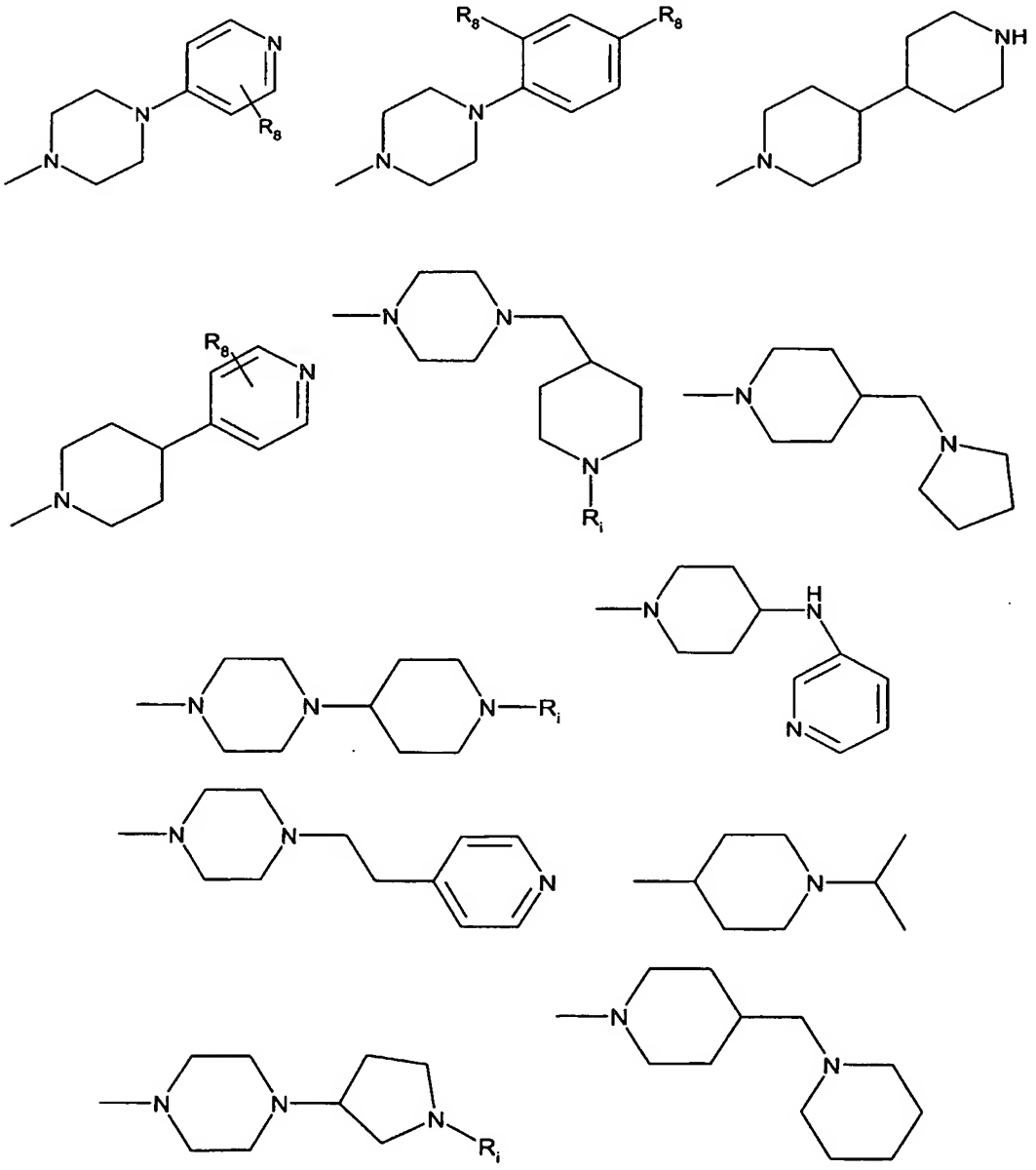
Z_1 is NH, Z_2 is N, h is 1.

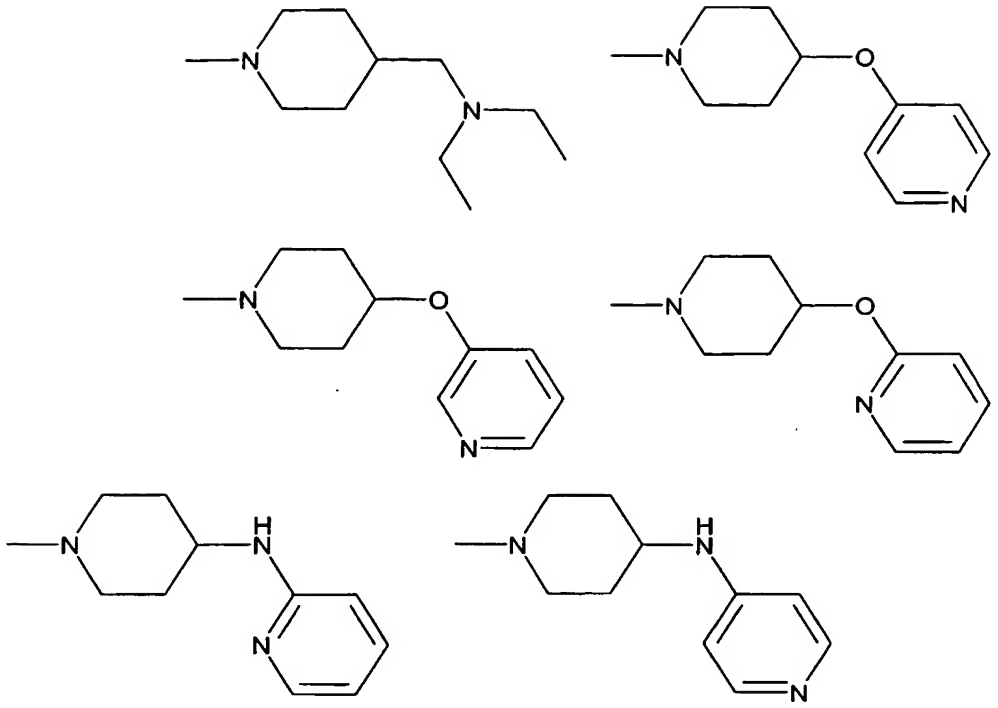
One group of lipophilic groups Lp that has been found to be associated with Factor Xa inhibitor activity is that of formula



in which L_x represents O or NH.

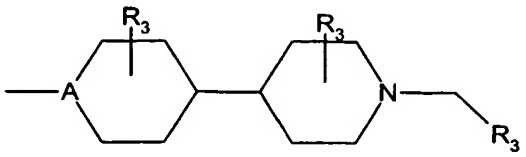
Examples of specific lipophilic groups of interest in Factor Xa inhibitors include





where R_8 is as defined for R_3 (preferably as defined for a substituent on an aromatic ring), especially where R_8 represents H, OMe, SO_2Me, F, cyano, amido, amino, NO_2, Cl or OH; and R_i is hydrogen or (1-6C)alkyl (such as methyl, ethyl or 2-propyl).

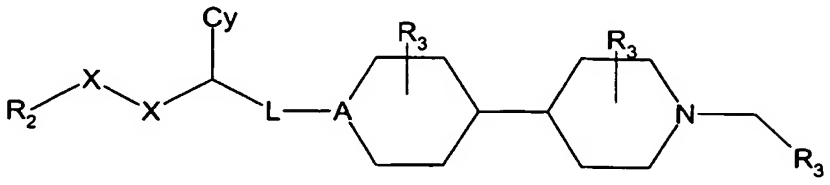
Another highly preferred lipophilic group in compounds of interest as Factor Xa inhibitors is of formula (DP)



(DP)

wherein A represents N or CH (preferably N) and R_3 is as hereinbefore defined. When the lipophilic group is (DP) it is preferred that the group L represents CO, CH_2 or SO_2. Also, it is preferred if the R_3 groups in the formula DP are hydrogen.

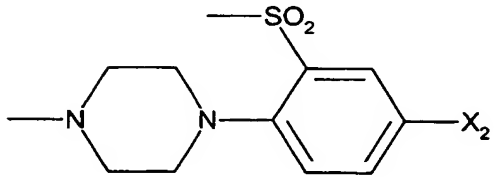
Hence, preferred compounds of formula (I) for use as Factor Xa inhibitors are those of formula (J)



(J)

where R_2, X-X, and Cy are as hereinbefore defined and L represents CO, CH_2 or SO_2.

Another highly preferred lipophilic group in Factor Xa inhibitors is based on the formula (K)

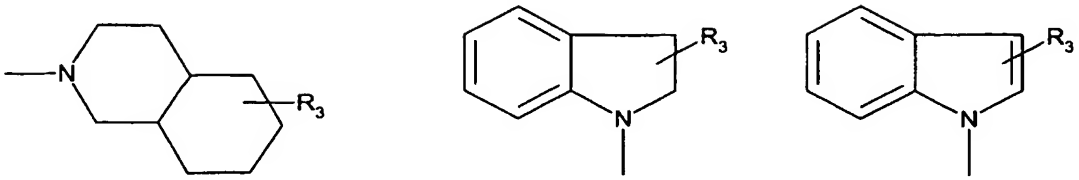


(K)

wherein X_2 is halo, hydrogen, amino, nitro or $CONH_2$.

Preferably X_2 is hydrogen or fluoro. Compounds in which the lipophilic group is based on the formula (K) or (J) have been found to perform relatively well in the prothrombin time assay, when compared with corresponding aminoisoquinolines of WO99/11657.

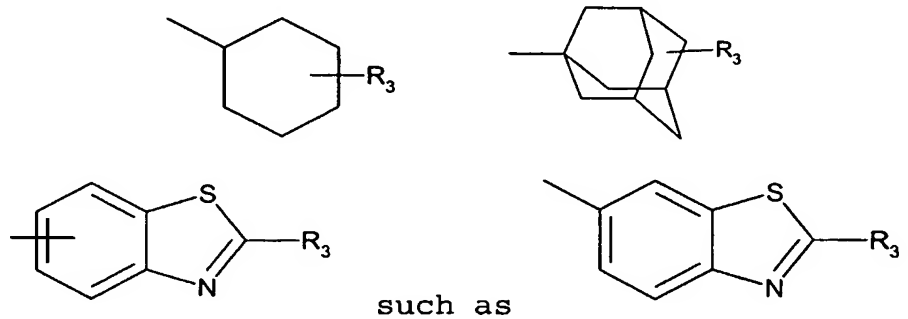
One group of compounds of particular interest as tryptase inhibitors is that in which L represents CO and Lp represents



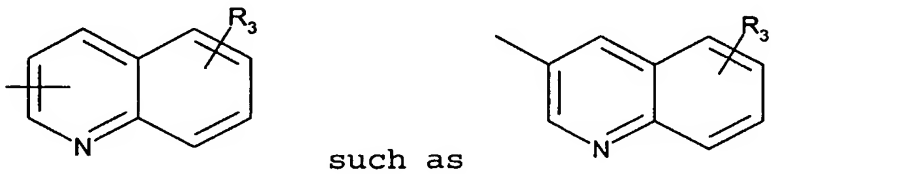
In this group of compounds, R_3 preferably represents hydrogen, hydroxyl or alkylaminocarbonyl.

Examples of particular values for Lp in this sub-group are pyrrolidin-1-yl, piperidin-1-yl, 3-N-methyl, N-ethylaminocarbonylpiperidin-1-yl, decahydroisoquinolin-2-yl and 2,3-dihydroindol-1-yl.

Another group of compounds of particular interest as tryptase inhibitors is that in which L represents CONH and Lp represents



such as



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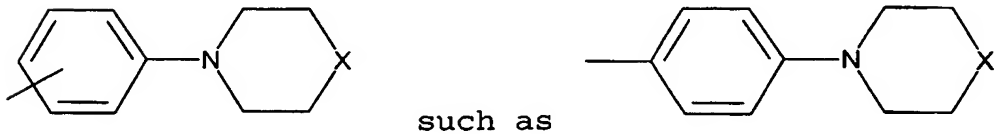

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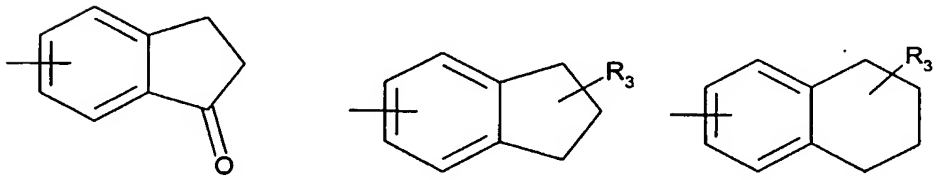

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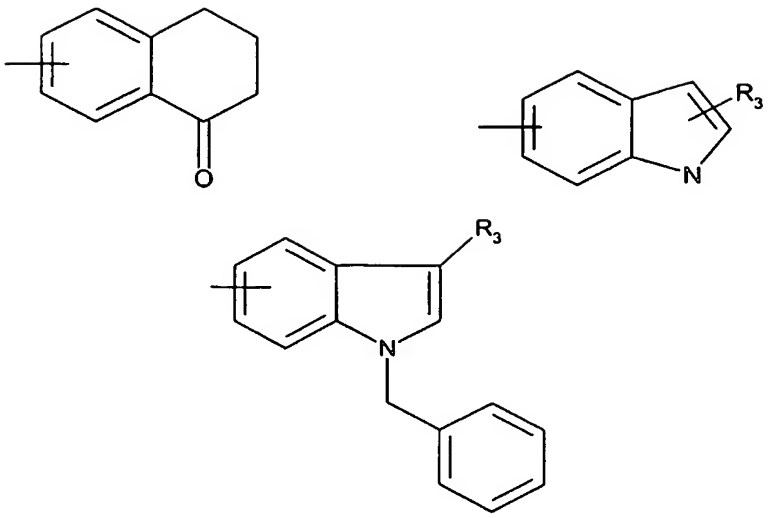


in which X is CH or N.

In this group of compounds, R_3 is preferably hydrogen, amino, hydroxy, alkyl or aminoalkyl.

Examples of particular values are:

(i) 2-aminocyclohexyl or 4-aminomethylcyclohexyl;

(ii) adamantyl;

(iii) 2-aminobenzothiazol-6-yl;

(iv) quinolin-3-yl;

(v) 4-piperidin-1-ylphenyl or 4-piperazin-1-ylphenyl;

(vi) 1-oxoindan-5-yl;

(vii) indan-5-yl;

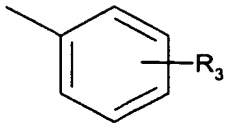
(viii) tetrahydronaphth-6-yl or 1-methyltetrahydronaphth-6-yl;

(ix) 1-oxotetrahydronaphth-6-yl or 1-oxotetrahydronaphth-7-yl;

(x) 2,3-dimethylindol-5-yl; and

(xi) (N-benzyl-3-acetylindol-5-yl or N-benzyl-3-acetylindol-7-yl.

Another group of compounds of particular interest as tryptase inhibitors is that in which L represents CONH and Lp represents

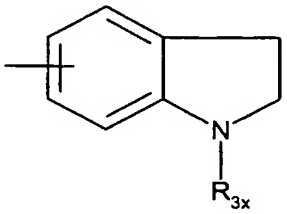


in which R_3 is alkylaminocarbonyl, N-alkylaminoalkanoyl, N-alkanoylaminoalkanonyl, C-hydroxyaminoalkanoyl, hydrogen, alkoxy, alkyl, aminoalkyl, aminocarbonyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl, alkylamino, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy or haloalkyl.

Preferably the phenyl group is unsubstituted or substituted by one or two R_3 groups.

Examples of particular values are phenyl, 3-cyano-4-methylphenyl, 3-aminocarbonylphenyl, 4-aminocarbonyl-phenyl, 4-chloro-3-aminocarbonyl-phenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 3-aminomethylphenyl, 4-methyl-3-acetylaminophenyl, 4-(1-hydroxethyl)phenyl and 4-isopropylphenyl.

Another particular group of compounds of formula I of interest as tryptase inhibitors is that in which L represents CONH and Lp represents



in which R_{3x} represents R_3 or a group of formula

$$-(CO)_p-(G_1)-R_j$$

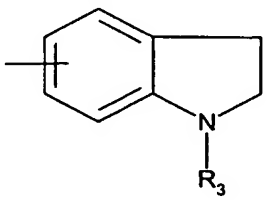
in which p is 0 or 1; G_1 represents (1-3C)alkanediyl or, when p is 1, a bond; and R_j represents a carbocyclic or heterocyclic group, optionally substituted by R_3.

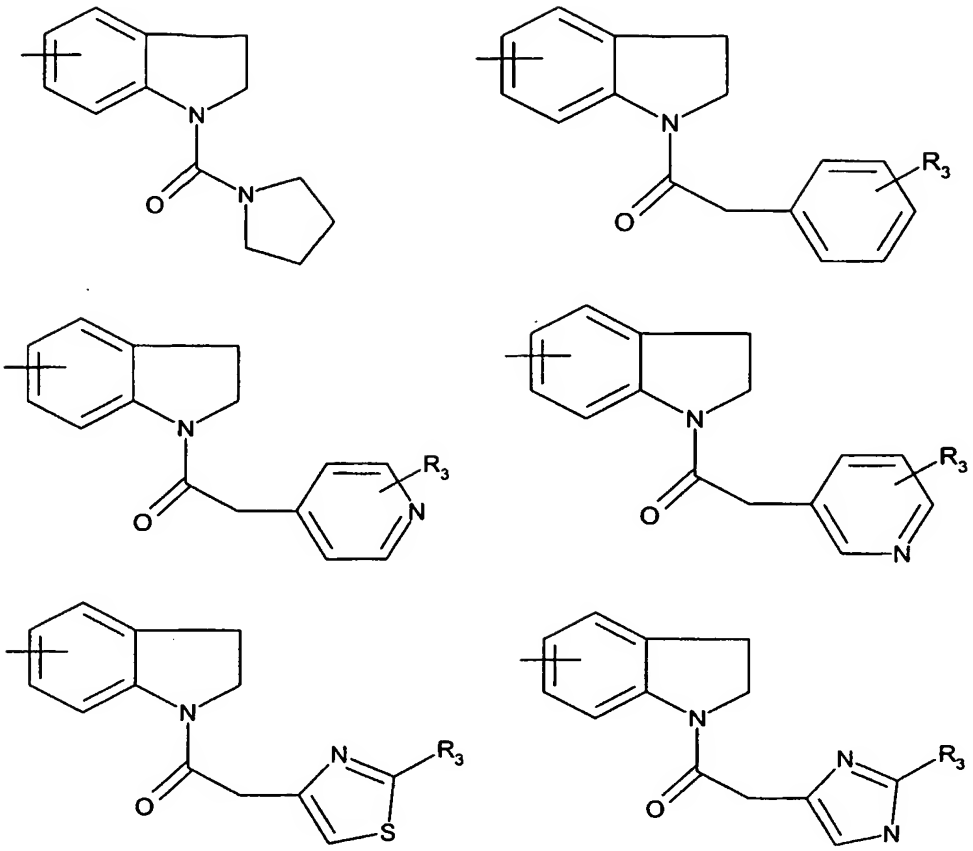
It will be appreciated that when Lp represents a group as described above, it corresponds to a group in which Lp is a combination of a heterocyclic group (2,3-dihydroindolyl), a carbocyclic or heterocyclic group (R_j) and optionally an alkyl group (G_1), which groups are linked by a single bond or a carbonyl group. Accordingly, examples of particular values for R_j are the examples given above for a carbocyclic or heterocyclic group forming part of Lp. Particular mention may be made of pyyrolidinyl, such as pyrrolidin-1-yl, phenyl, thiazolyl, such as thiazol-4-yl, imidazolyl, such as imidazol-4-yl, and pyridyl, such as pyrid-2-yl, pyrid-3-yl and pyrid-4-yl.

Examples of values for G are $-CH_2-$, and CH_2CH_2.

The 2,3-dihydroindolyl group in the above formula is preferably a 2,3-dihydroindol-5-yl or -6-yl group, especially a 2,3-dihydroindol-6-yl group.

Examples of structures of compounds comprising a 2,3-dihydroindolyl group as described above are:





When R_3 is a substituent on the 1-position of a 2,3-dihydroindolyl group, it preferably represents alkylaminocarbonyl; N-alkylaminoalkanoyl; N-alkanoylaminoalkanonyl; C-hydroxyaminoalkanoyl; hydrogen; alkyl; alkanoyl; alkoxycarbonyl; acyloxymethoxycarbonyl; aminoalkyl; aminoalkanoyl; hydroxyalkyl; hydroxyalkanoyl; alkoxyalkyl; or alkanoylamino. Examples of particular values are: N-methylaminoacetyl, N-acetylaminoacetyl, N-acetylalaninoyl, serinoyl, threoninoyl, hydrogen, methyl, acetyl, propanoyl, 2-methylpropanoyl, 3-methylbutyryl, 2-hydroxypropanoyl, hydroxyacetyl, aminoacetyl and alaninoyl.

Accordingly, examples of particular values for Lp are: 1-(N-methylaminoacetyl)-2,3-dihydroindol-6-yl; 1-(N-acetylaminoacetyl)-2,3-dihydroindol-6-yl; 1-(N-acetylalaninoyl)-2,3-dihydroindol-6-yl; 1-(serinoyl)-2,3-

dihydroindol-6-yl; 1-(threoninoyl)-2,3-dihydroindol-6-yl; 2,3-dihydroindol-5-yl; 1-methyl-2,3-dihydroindol-6-yl; 1-acetyl-2,3-dihydroindol-6-yl; 1-propanoyl-2,3-dihydroindol-6-yl; 1-(2-methylpropanoyl)-2,3-dihydroindol-6-yl; ; 1-(3-methylbutyryl)-2,3-dihydroindol-6-yl; 1-(2-hydroxpropanoyl)-2,3-dihydroindol-6-yl; 1-hydroxacetyl-2,3-dihydroindol-6-yl; 1-aminoacetyl-2,3-dihydroindol-6-yl and 1-alaninoyl-2,3-dihydroindol-6-yl.

When R_3 is a substituent on a phenyl, thiazolyl, imidazolyl or pyridyl group, it is preferably hydrogen, amino, alkyl or aminoalkyl. Examples of particular values are hydrogen, amino, alkyl or aminomethyl.

Accordingly, further examples of particular values for Lp are: 2,3-dihydroindol-5-yl, 1-prolinoyl-2,3-dihydroindol-6-yl, 1-phenylacetyl-2,3-dihydroindol-6-yl, 1-(2-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(3-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(4-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(4-pyridyl)acetyl-2,3-dihydroindol-6-yl, 1-(3-pyridyl)acetyl-2,3-dihydroindol-6-yl, 1-imidazol-4-ylacetyl-2,3-dihydroindol-6-yl, 1-(2-aminothiazol-4-yl)acetyl-2,3-dihydroindol-6-yl, and 1-(2-formamidothiazol-4-yl)acetyl-2,3-dihydroindol-6-yl.

The hydrogen bond donor group which may be attached to the lipophilic group preferably has a nitrogen or oxygen atom as the hydrogen bearing donor atom and conveniently is a hydroxyl group, a primary, secondary or tertiary amine, or a primary or secondary imine group (as part of an amidine or guanidine) or a saturated or unsaturated heterocyclic group containing a ring nitrogen, preferably a group containing 5 to 7 ring atoms. Where the donor atom is a ring nitrogen,

the remote portion of the heterocyclic ring may be part of the lipophilic group.

The cyclic group attached to the alpha carbon is preferably an optionally R_{3a} substituted phenyl, pyridyl (such as pyrid-2-yl, pyrid-3-yl or pyrid-4-yl), thienyl (such as thien-2-yl or thien-3-yl), thiazolyl (such as thiazol-2-yl, thiazol-4-yl or thiazol-5-yl), naphthyl (such as naphth-1-yl), piperidinyl (such as piperidin-4-yl) or cycloalkyl, such as a cyclohexyl group.

Examples of particular values for R_{3a} are:-

hydrogen;

hydroxyl;

for alkoxy: methoxy or ethoxy;

for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkylaminoalkyl, such as methylaminomethyl or dimethylaminomethyl;

for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: hydroxymethyl or carboxy;

for alkoxyalkyl: methoxymethyl;

for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl;

for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;

for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, $CONH_2$, CH_2CONH_2 or aminoacetyl;

for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkanoylamino, such as formylamino or acetylamino;

for alkoxycarbonylamino: methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino;

amino;
for halo: fluoro or chloro;
cyano;
nitro;
thiol;
for alkylthio: methylthio;
for alkylsulphonyl: methylsulphonyl or ethylsulphonyl;
for alkylsulphenyl: methylsulphenyl;
for imidazolyl: imidazol-4-yl;
hydrazido;
for alkylimidazolyl: 2-methylimidazol-4-yl;
for alkylsulphonamido: methylsulphonylamido or ethylsulphonylamido;
for alkylaminosulphonyl: methylaminosulphonyl or ethylaminosulphonyl;
aminosulphonyl;
for haloalkoxy: trifluoromethoxy; and
for haloalkyl: trifluoromethyl.

Examples of particular values for R_{1c} are:
hydrogen;
hydroxyl;
for alkoxy: methoxy or ethoxy;
for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkylaminoalkyl, such as methylaminomethyl or dimethylaminomethyl;
for hydroxyalkyl: hydroxymethyl;
for alkoxyalkyl: methoxymethyl;
for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl;
for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;

for alkoxycarbonylamino: methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino; for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkanoylamino, such as formylamino or acetylamino; and for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, $CONH_2$, CH_2CONH_2 or aminoacetyl.

Cy is preferably unsubstituted or substituted by one or two R_{3a} groups.

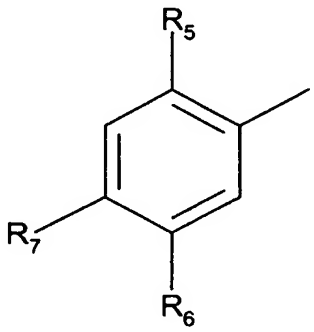
Preferably R_{3a} is hydrogen, hydroxyl, methoxy, methyl, amino, aminomethyl, hydroxymethyl, formylamino, acetylamino, aminoacetyl, fluoro, chloro, ethylsulphonylamino, amido or methylaminocarbonyl.

Examples of particular values for Cy are phenyl, 4-aminophenyl, 4-amidophenyl, 4-(N-methyl)amidophenyl, 4-(N,N-dimethyl)amidophenyl, 2-chlorophenyl, 2-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-aminomethylphenyl, 4-aminomethylphenyl, 2-hydroxymethylphenyl, 3-hydroxymethylphenyl, 4-hydroxymethylphenyl, 4-carboxyphenyl, 3-ethylsulphonylaminophenyl, thien-2-yl, thien-3-yl, thiazol-4-yl, thiazol-5-yl, 2-methylthiazol-4-yl, 2-aminothiazol-4-yl, 2-formylaminothiazol-4-yl, 2-aminothiazol-5-yl, 2-formylaminothiazol-5-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 4-aminopyrid-3-yl, 4-aminopyrid-4-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, cyclohexyl and naphth-1-yl.

Referring to the group R_2, examples of a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom are phenyl; pyrrolyl, such as 2-pyrrolyl; pyridyl, such as 3-pyridyl; pyrazinyl,

such as 2-pyrazinyl; furyl, such as 2-furyl; and thienyl, such as 2-thienyl or 3-thienyl. Preferably the ring is interrupted (i.e. a carbon atom is replaced) by at most one heteroatom. More preferably the ring is phenyl, 2-thienyl or 2-pyrrolyl. Most preferably, the ring is phenyl.

When the ring is phenyl, the group R_2 may be a group of formula



in which R_5 is amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen, and R_6 and R_7 which may be the same or different represent halo, nitro, thiol, cyano, haloalkyl, haloalkoxy, amido, hydrazido, amino, alkylthio, alkenyl, alkynyl or R_1 or taken together form a 5 or 6 membered fused carbocyclic ring or 5 membered heterocyclic ring, which may itself be substituted by R_{1j}, amino, halo, cyano, nitro, thiol, alkylthio, haloalkyl, haloalkoxy.

When the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring, examples of the resultant bicyclic ring are naphthyl, such as 2-naphthyl; benzimidazolyl, such as benzimidazol-5-yl or benzimidazol-6-yl; isoquinolinyl, such as isoquinolin-7-yl; indolyl, such as indol-2-yl, indol-5-yl or indol-6-yl; indazolyl, such as indazol-5-yl; indazol-6-yl; 3,4-methylenedioxyphenyl; dihydroindolyl, such as 2,3-dihydroindol-6-yl; benzothiazolyl, such as benzothiazol-2-yl or benzothiazol-6-

yl; benzo[b]thiophenyl, such as benzo[b]thiophen-2-yl; benzofuryl, such as benzofur-2-yl; imidazo[1,2-a]pyrimidinyl, such as imidazo[1,2-a]pyrimidin-2-yl; tetrahydroimidazo[1,2-a]pyrimidinyl, such as tetrahydroimidazo[1,2-a]pyrimidin-2-yl; and benzisoxazolyl, such as benzisoxazol-5-yl.

R_2 preferably represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, and optionally substituted at the 6 position by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(ii) naphth-2-yl optionally substituted at the 6 or 7 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j} and optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j};

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_1;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_1;

(ix) pyrid-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_1;

(x) pyrid-3-yl optionally substituted at the 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_1;

(xi) benzofur-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j};

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by alkyl and optionally substituted at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j};

(xiii) indol-6-yl substituted at the 5 position by amino, hydroxy, halo (such as fluoro or chloro), alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio and optionally substituted at the 3 position by halo (such as chloro), haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}; or

(xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5

or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}.

Examples of particular values for substituents that may be present on R_2 are:

for halo: fluoro, chloro, bromo or iodo;

nitro;

thiol;

for haloalkoxy: difluoromethoxy or trifluoromethoxy;

hydrazido;

for alkylhydrazido: methylhydrazido;

amino;

cyano;

for haloalkyl: trifluoromethyl;

for alkylthio: methylthio;

for alkenyl: vinyl;

for alkynyl: ethynyl;

for acylamino: acetylamino;

carboxy;

for acyloxy: acetoxy;

hydroxy;

for alkyl: methyl or ethyl;

amido ($CONH_2$);

for aminoalkyl: aminomethyl; and

for alkoxy: methoxy or ethoxy.

Examples of particular values for R_1 are:

hydrogen;

hydroxy;

for alkoxy: methoxy or ethoxy;

for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, alkylaminoalkyl, such as dimethylaminomethyl, or alkanoyl, such as acetyl;

for hydroxyalkyl: hydroxymethyl;
for alkoxyalkyl: methoxymethyl;
for alkoxycarbonyl: methoxycarbonyl;
for alkylaminocarbonyl: methylaminocarbonyl;
for alkylamino: methylamino, ethylamino or dimethylamino;
for hydroxyalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: carboxyl or carboxymethyl; and
for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: amido ($CONH_2$) or amidomethyl.

Examples of particular values for R_{1j} are:
hydrogen;
hydroxy;
for alkoxy: methoxy or ethoxy;
for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkanoyl, such as acetyl;
for hydroxyalkyl: hydroxymethyl;
for alkoxyalkyl: methoxymethyl;
for alkoxycarbonyl: methoxycarbonyl;
for alkylamino: methylamino, ethylamino or dimethylamino;
for hydroxyalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: carboxyl or carboxymethyl; and
for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: amido ($CONH_2$) or amidomethyl.

More preferably R_2 represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by fluoro, chloro, bromo, iodo, nitro, difluoromethoxy, trifluoromethoxy, amino, cyano, trifluoromethyl, methylthio, vinyl, carboxy, acetoxy, $MeSO_2$-, hydroxy, methoxy, ethoxy, methyl, aminomethyl, methoxycarbonyl, methylamino, ethylamino or amido, and optionally substituted at the 6 position by amino, hydroxy,

fluoro, methoxycarbonyl, cyano or aminomethyl (preferably phenyl substituted in the 4 position by chloro, amino, vinyl, methylamino, methyl or methoxy, optionally at the 3 position with amino or hydroxy, and optionally at the 6 position with amino or hydroxy);

(ii) naphth-2-yl optionally substituted at the 6, position by hydroxy and optionally substituted at the 3 position by amino or hydroxy;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by chloro, bromo, amino, methyl or methoxy (preferably indol-6-yl optionally substituted at the 3 position by chloro, bromo, methyl or methoxy);

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by methylthio, methyl or acetyl;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl substituted at the 5 position by methyl;

(ix) pyrid-2-yl optionally substituted at the 6 position by chloro;

(x) pyrid-3-yl optionally substituted at the 4 position by chloro;

(xi) benzofur-2-yl optionally substituted at the 3 position by chloro, methyl or methoxy, at the 5 or 6 position by methyl and at the 6 position by methoxy;

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by methyl and optionally substituted at the 5 or 6 position by fluoro, chloro, bromo, methyl or methoxy;

(xiii) indol-6-yl substituted at the 5 position by chloro, fluoro or hydroxy and optionally substituted at the 3 position by chloro or methyl; or

(xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by fluoro, chloro or methyl, and optionally substituted at the 5 or 6 position by fluoro, chloro, methyl, hydroxy, or methoxy.

Examples of particular values for R_2 are:

(i) phenyl, 2-aminophenyl, 3-aminophenyl, 2-amino-3-fluorophenyl, 2-amino-4-fluorophenyl, 2-amino-4-chlorophenyl, 2-amino-3-bromophenyl, 2-amino-3-nitrophenyl, 2-amino-4-nitrophenyl, 3,4-dimethoxy-5-aminophenyl, 2-amino-4-methylphenyl, 2-amino-3-methylphenyl, 2-amino-3-methoxyphenyl, 3,4-diaminophenyl, 3,5-diaminophenyl, 3-amino-4-fluorophenyl, 3-amino-4-chlorophenyl, 3-amino-4-bromophenyl, 3-amino-4-hydroxyphenyl, 3-amino-4-carboxymethylphenyl, 3-amino-4-methylphenyl, 3-amino-4-methoxyphenyl, 2-fluorophenyl, 4-fluoro-3-cyanophenyl, 3-chlorophenyl, 3-chloro-4-hydroxphenyl, 3-chloro-5-hydroxyphenyl, 4-chlorophenyl, 4-chloro-2-hydroxyphenyl, 4-chloro-3-hydroxyphenyl, 4-chloro-3-methylphenyl, 4-chloro-3-methoxyphenyl, 4-bromophenyl, 4-bromo-3-methylphenyl, 4-iodophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-cyano-5-aminophenyl, 2-hydroxphenyl, 2-hydroxy-4-methoxyphenyl, 3-hydroxphenyl, 3-hydroxy-4-methylphenyl, 2,4-dihydroxyphenyl, 3,4-dihydroxyphenyl, 3-hydroxy-4-methoxyphenyl, 4-difluoromethoxyphenyl, 4-trifluoromethoxphenyl, 4-trifluoromethylphenyl, 4-methylthiophenyl, 4-methoxycarbonylphenyl, 4-acetoxyphenyl,

4-methanesulfonylphenyl, 3-methylphenyl, 3-aminomethylphenyl, 3-aminomethyl-6-aminophenyl, 3-methyl-5-aminophenyl, 4-methylphenyl, 4-vinylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-methoxy-3-chlorophenyl, 4-methoxy-3-methylphenyl, 3-methylaminophenyl, 4-methylaminophenyl, 4-ethylaminophenyl or 2-aminomethylphenyl;

(ii) naphth-2-yl, 3-aminonaphth-2-yl, 3-hydroxynaphth-2-yl or 6-hydroxynaphth-2-yl;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, 3-chloroindol-6-yl, 3-bromoindol-6-yl, 3-methylindol-6-yl, 3-methoxyindol-6-yl, indazol-5-yl, 3-aminoindazol-5-yl, indazol-6-yl, benzothiazol-6-yl, 3-aminobenzisoxazol-5-yl;

(iv) benzimidazol-5-yl, 2-aminobenzimidazol-5-yl, or benzothiazol-6-yl;

(v) thien-2-yl, 5-methylthien-2-yl, 5-methylthio-thien-2-yl, 5-acetylthien-2-yl or thien-3-yl;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) 5-methylpyrazol-2-yl;

(ix) 5-chloropyrid-2-yl;

(x) pyrid-3-yl, 6-chloropyrid-3-yl;

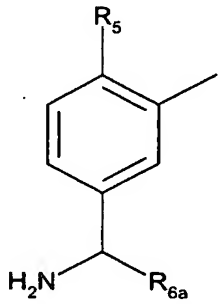
(xi) benzofur-2-yl, 5-chlorobenzofur-2-yl, 3-methylbenzofur-2-yl, 5-methylbenzofur-2-yl,. 6-methoxybenzofur-2-yl;

(xii) indol-2-yl, 5-fluoroindol-2-yl, 5-chloroindol-2-yl, 5-methylindol-2-yl, 5-methoxindol-2-yl, 6-methoxyindol-2-yl and 1-methyl-indol-2-yl;

(xiii) 5-fluoroindol-6-yl; or

(xiv) benzo[b]thiophen-2-yl, 5-chloro-benzo[b]thiophen-2-yl or 6-chlorobenzo[b]thiophen-2-yl.

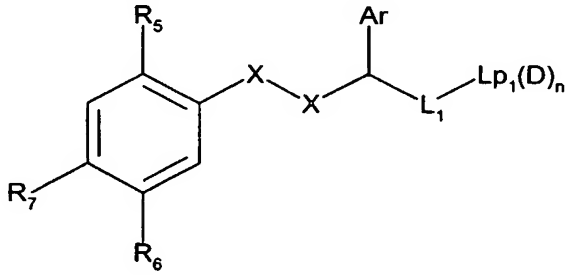
It has been found that in compounds of formula (I) that have been found to be tryptase inhibitors, the aromatic R_2 group is of the formula



in which R_5 is amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen, and R_{6a} is hydrogen or methyl.

For a tryptase inhibitor, preferably R_2 is 3-aminomethylphenyl or 3-aminomethyl-6-aminophenyl. Most preferably it is 3-aminomethylphenyl.

In one embodiment the aromatic R_2 group is an optionally substituted phenyl, naphthyl, indolyl or isoindolyl group and accordingly, preferred compounds of formula (I) are of formula (II)



(II)

wherein R_5 is amino, hydroxy or hydrogen, and R_6 and R_7 which may be the same or different represent halo, nitro, thiol, cyano, haloalkyl, haloalkoxy, amido, hydrazido, amino, alkylthio, alkenyl, alkynyl or R_1 or taken together form a 5 or 6 membered fused carbocyclic ring or 5 membered

heterocyclic ring, which may itself be substituted by R_{1j}, amino, halo, cyano, nitro, thiol, alkylthio, haloalkyl, haloalkoxy;

Ar is an unsubstituted or substituted aryl group, preferably phenyl;

X-X is -CONH-, $-CH_2CH_2-$, CH_2O-, -COO-, $-CH_2NH-$, $-OCH_2-$ or $-NHCH_2-$, especially -CONH-;

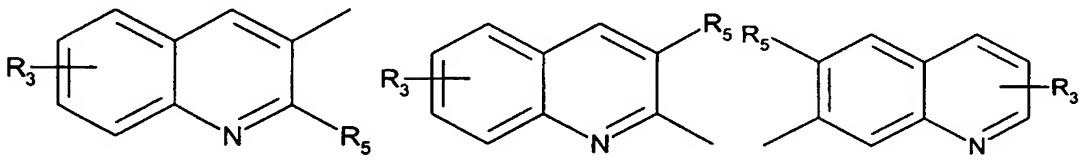
L_1 is a valence bond or an organic linker group containing 1 to 4 backbone atoms selected from C, N, O and S;

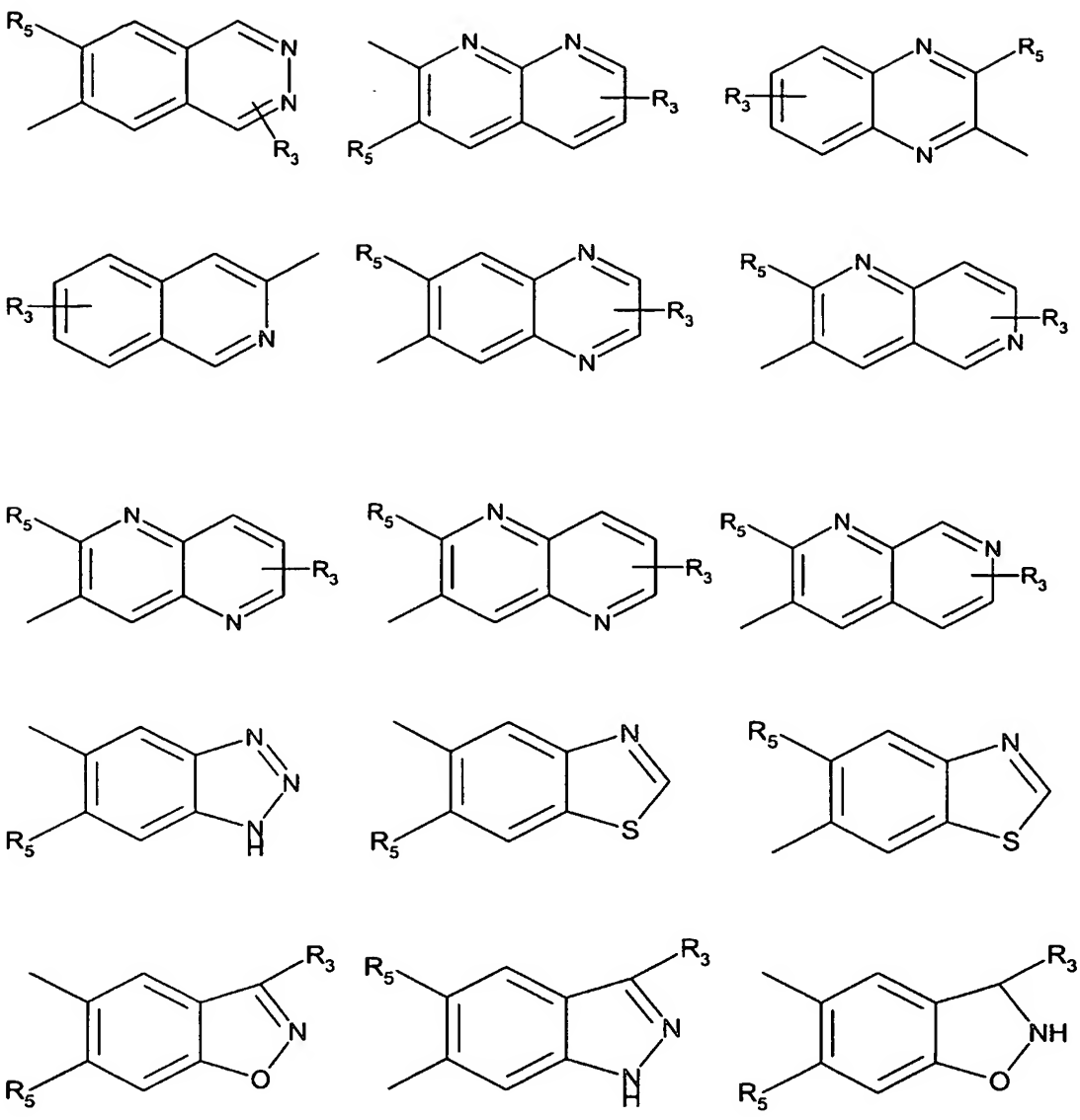
Lp_1 is a cycloalkyl, azacycloalkyl, diazacycloalkyl, phenyl, naphthyl, adamantyl, decalinyl, bicycloalkyl, mono- or diazabicycloalkyl, mono- or bicyclo heteroaromatic or a linear or branched alkyl, alkylene, alkenyl or alkenylene group all optionally substituted by a group R_3, or a combination of at least two such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO_2, $CONR_{1e}$, $NR_{1e}-CO-$, NR_{1e} linkage (for example, representative lipophilic groups include a methyl-cyclohexyl, methylcyclohexylmethyl, bispiperidinyl, methylphenylmethyl, phenylethyl, benzylpiperidinyl, benzoylpiperidinyl or phenylpiperazinyl and those as hereinbefore described);

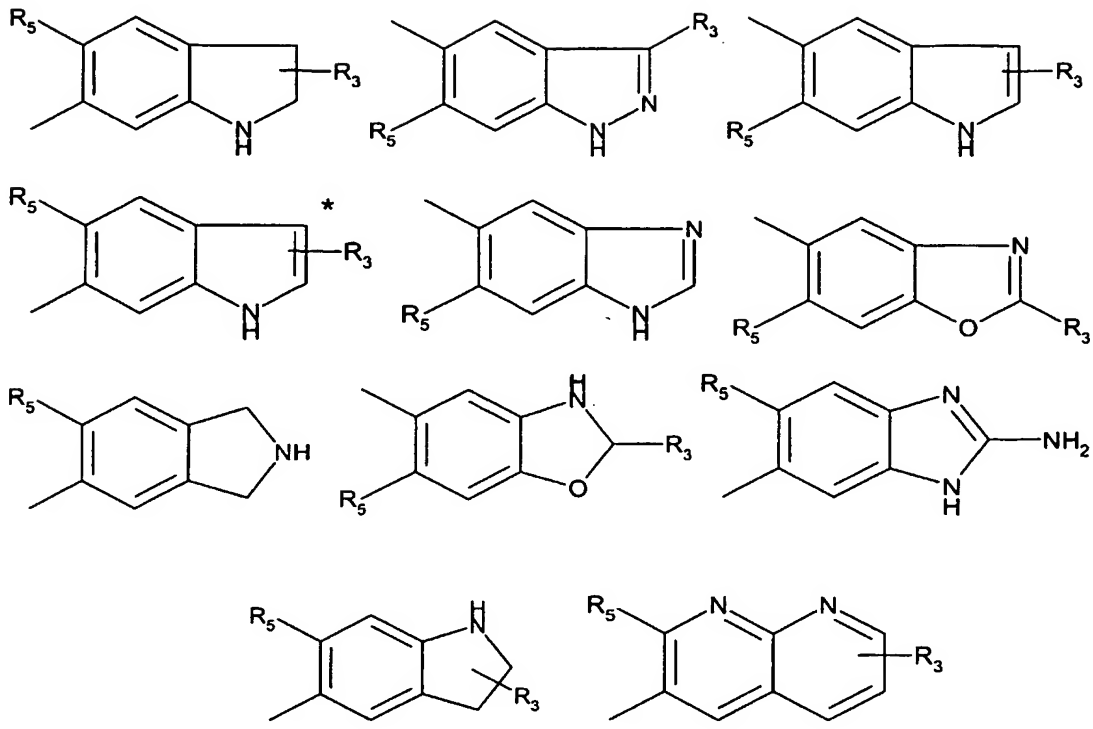
D is a hydrogen bond donor group;

and n is 0, 1 or 2.

Suitable R_2 groups may be







wherein R_5 is hydrogen, amino or hydroxy and R_3 (in relation to R_2) is halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}.

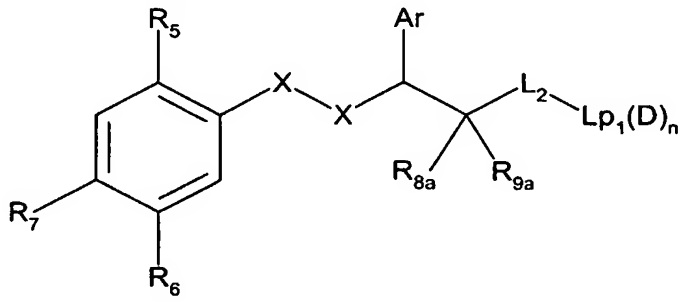
In a particularly favoured embodiment the R_2 group is an indole as marked by a * above in which R_5 is hydrogen and R_3 is a hydrogen or halogen present at the 3 position.

It is preferred that at least one of R_6 and R_7 be other than hydrogen and that R_6, if present, is preferably a substituent containing one or more polar hydrogens such as hydroxy, amino, alkylamino, aminoalkyl, alkylaminoalkyl, aminocarbonyl, alkylaminocarbonyl, hydrazo and alkylhydrazo; alternatively R_6 and R_7 are joined together in the formation of a naphthyl or indolyl or azaindolyl or diazaindolyl group.

It is especially preferred that R_6 be amino and R_7 be chloro, bromo, methyl, methoxy or vinyl; or that R_6 and R_7

taken together form an indolyl ring with the NH at the 6-position or taken together form a naphthyl ring.

In a further preferred embodiment the compounds of formula (I) are of formula (A)



(A)

(wherein R_5, R_6, R_7, Ar, X-X, Lp_1, D_n are as hereinbefore defined; L_2 is a valence bond or an organic linker group containing 1 to 3 backbone atoms selected from C, N, O and S and R_{8a} and R_{9a} are hydrogen or taken together with the carbon atom to which they are attached form a carbonyl group). Again, in an alternative embodiment the phenyl derivative forming part of the R_2 functionality may instead be a nitrogen heterocyclic group, e.g. pyridine.

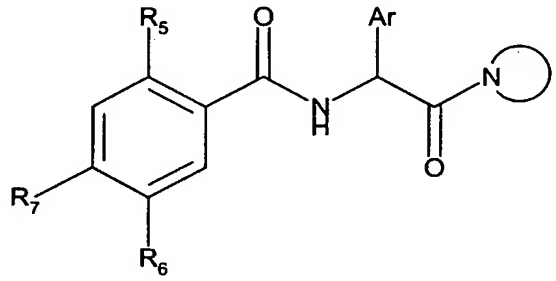
In one embodiment, L_2 comprises the backbone of an alpha amino acid, the lipophilic group being the side chain of the amino acid.

In one preferred embodiment R_{8a} and R_{9a} are hydrogen and L_2 is a OC=O or NHC=O group.

In a preferred embodiment, L_2 represents a valence bond and the lipophilic group is bound directly to a carbonyl alpha to the alpha atom via a nitrogen atom which forms part of the lipophilic group. Suitable lipophilic groups in this case therefore include piperidinyl, pyrrolidinyl and piperazinyl. In a preferred embodiment the piperidine or piperazinyl group is further substituted by a phenyl, benzyl, phenoxy, piperidine, pyridine or benzoyl group,

optionally substituted on the phenyl ring by one or more R_3 groups. In a more preferred embodiment a piperazine is substituted with a phenyl group substituted at the 2-position with an electron withdrawing group such as fluoro, nitro, triazolyl, cyano, alkoxycarbonyl, aminocarbonyl, aminosulphonyl, alkylaminosulphonyl and, especially preferred, alkylsulphonyl; and, at the 4-position, with hydrogen, fluoro, alkoxy or hydroxy. In another more preferred embodiment a piperidine is substituted at the 4-position with 4-piperidine which itself may be substituted on nitrogen by alkyl or aminocarbonylalkyl or alkylaminocarbonyl alkyl.

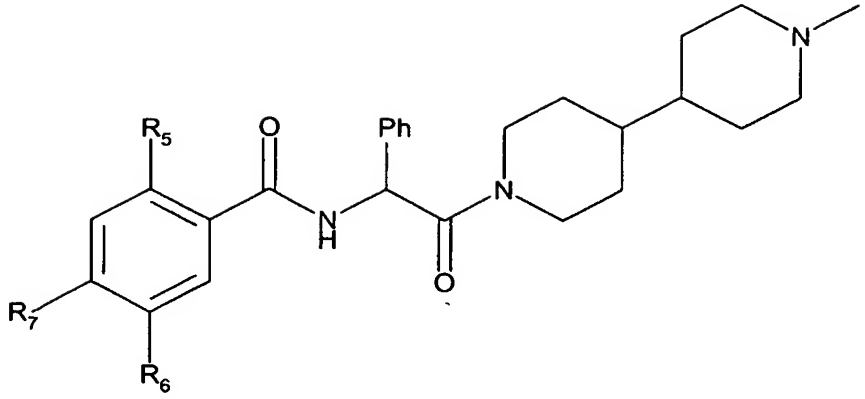
In a further embodiment, the lipophilic group has attached a group of the formula $-COOR_{1g}$ or -CON-aminoacid or ester derivative thereof (where R_{1g} is as defined for R_{1a}). Particularly preferred compounds are those of formula (G)



(G)

(wherein Ar, R_6 and R_7 are as hereinbefore defined, R_5 represents hydrogen or amino and

represents a cyclic group) or of formula (H)

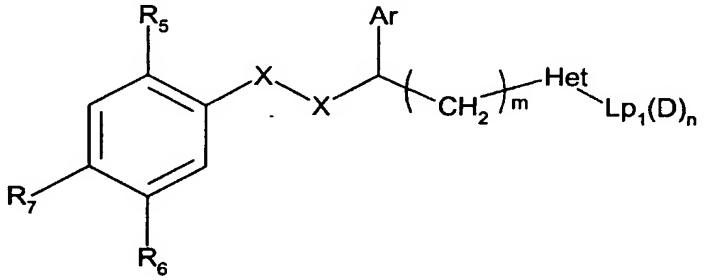


(H)

(wherein R_6 and R_7 are as hereinbefore defined, and R_5 represents hydrogen or amino). In a preferred embodiment R_6 is amino and R_7 a halogen, especially chlorine.

Again, in an alternative embodiment the phenyl derivative forming part of the R_2 functionality in formulae (G) and (H) may instead be a nitrogen heterocyclic group, e.g. pyridine, indole.

In another embodiment the group binding the alpha carbon atom to the lipophilic group comprises a heterocyclic group. Accordingly, preferred compounds of formula (I) also include those of formula (III)



(III)

(wherein R_5, R_6, R_7, Ar, X-X, Lp_1, D_n are as hereinbefore defined;

m is 0, 1 or 2;

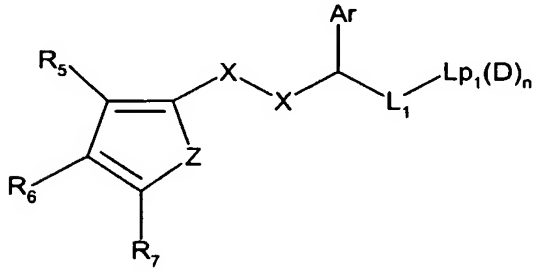
Het is a 5 or 6-membered heterocyclic group interrupted by 1, 2 or 3 heteroatoms selected from O, N and S optionally substituted by a group R_{3b} where R_{3b} is as defined for R_3).

Again, in an alternative embodiment the phenyl derivative forming part of the R_2 functionality may instead be a nitrogen heterocyclic group, e.g. pyridine.

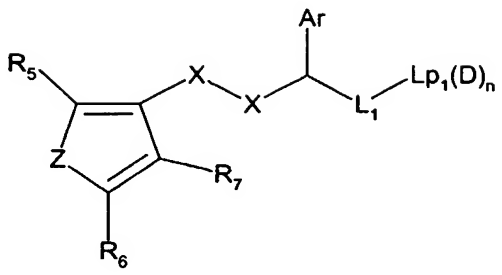
Where Het is a five membered ring, the two ring atoms at which it is connected are preferably separated by one ring atom. Where Het is a six-membered ring, the two ring atoms at which it is connected are preferably separated by one or two ring atoms. Representative heterocyclic groups include thiazole, oxazole, oxadiazole, triazole, thiadiazole or imidazole. Where the heterocyclic group is substituted by R_{3b} .this is preferably a COOH or $COOR_{1h}$ connected to the heterocycle via a valence bond or alkylene chain (where R_{1h} is as defined for R_{1a}).

In a further embodiment, the lipophilic group has attached a group of the formula $-COOR_{1g}$ or -CON-aminoacid or ester derivative thereof.

In an alternative embodiment, the main aromatic R_2 ring in the compounds of the invention is a five membered aromatic ring leading to compounds of formula (IV) or (IVa)

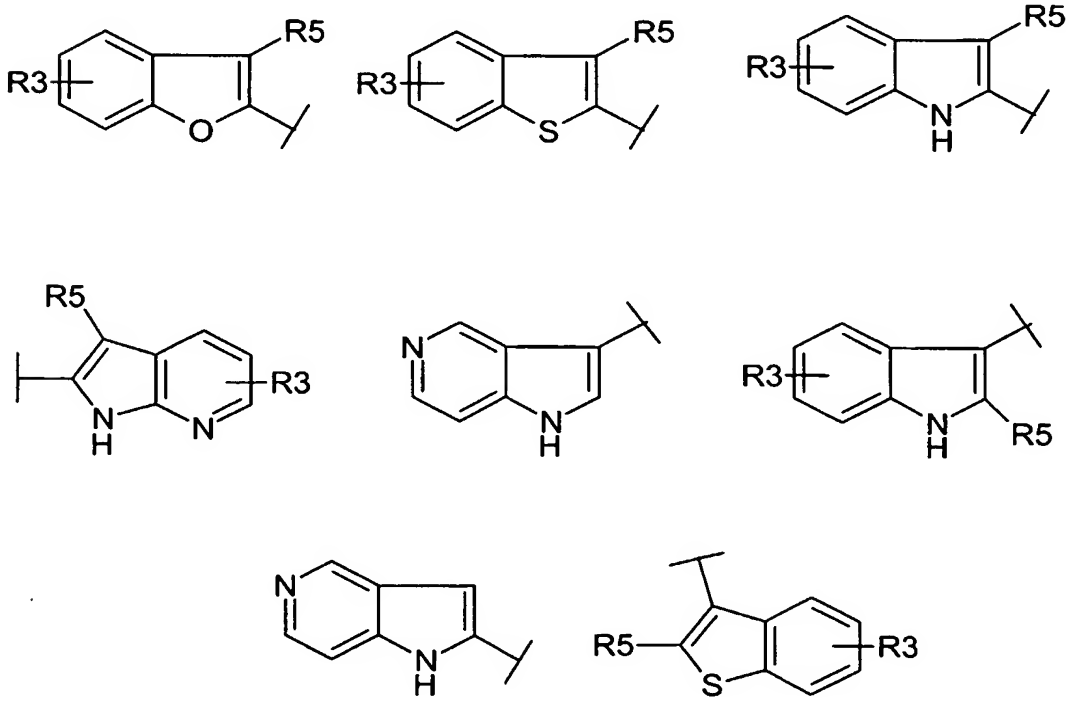


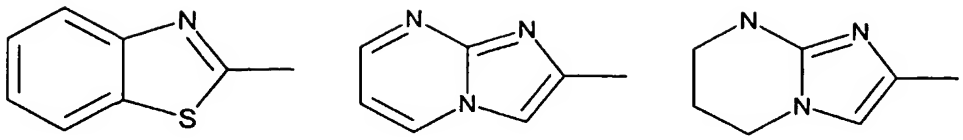
(IV)



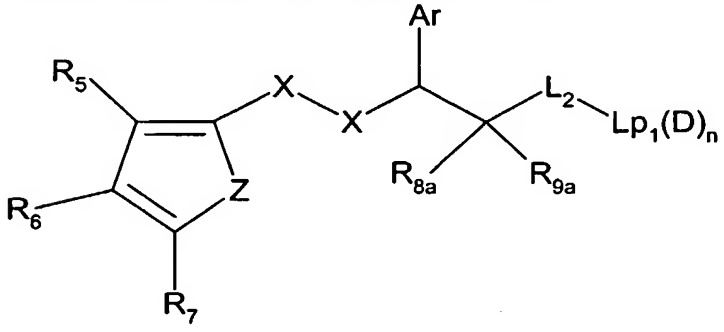
(IVa)

(wherein R_5, R_6, R_7, X-X, Ar, L_1, Lp_1, D and n are as hereinbefore described for formula (II) and Z represents N, O or S). It is preferred that at least one of R_6 and R_7 be other than hydrogen, or that R_6 and R_7 taken together enable the formation of an indolyl, or azaindolyl group or diazaindolyl group. Preferences for other substituents are as for formula (A) above. Examples of possible fused systems are given below.

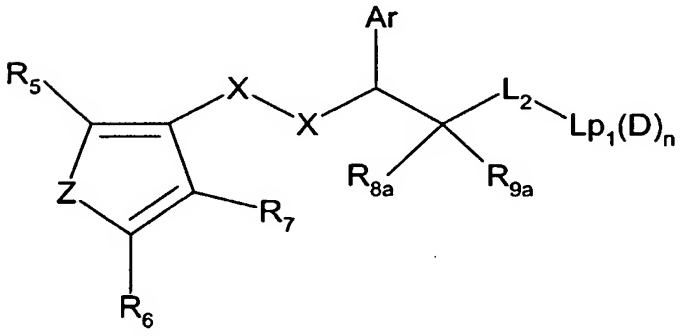




Hence in a preferred embodiment the compounds of the invention are of formula C or D

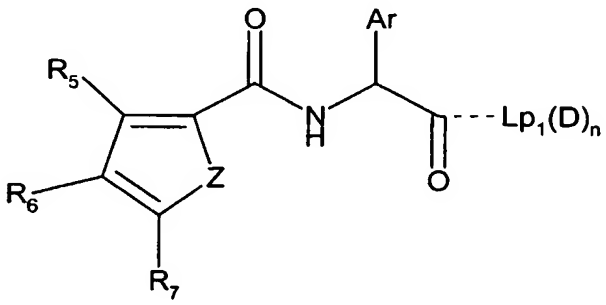


(C)

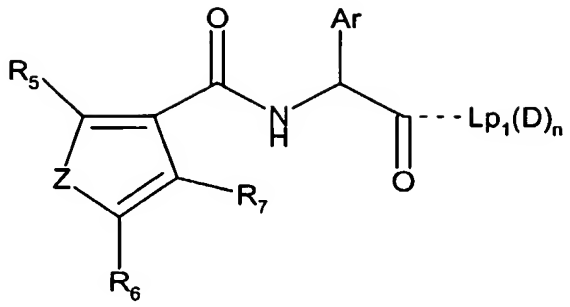


(D)

(wherein R_5, R_6, R_7, Ar, X-X, Z, R_8, R_9, L_2 Lp_1, D_n are as hereinbefore defined) preferences for Ar, X-X, R_{8a}, R_{9a}, L_2, Lp_1, D_n are as for formula (A) above; or compounds of formula E or F:



(E)

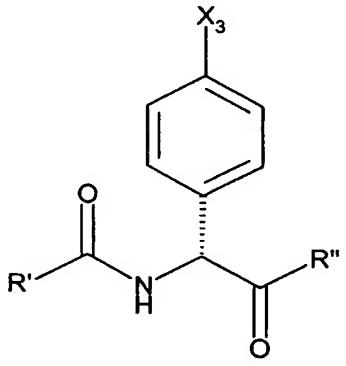


(F)

wherein Lp_1 is connected to the carbonyl via a nitrogen atom, R_6, R_7, Ar, Z, Lp_1, D_n are as hereinbefore defined and R_5 is hydrogen or amino) preferences for Ar, Lp_1, D_n are as for formula (A) above.

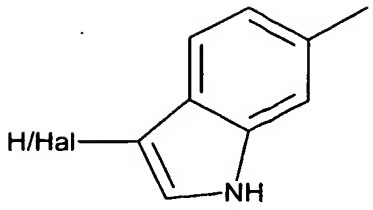
Particularly preferred compounds of formula (I) for use as Factor Xa inhibitors are the compounds of Examples 35, 63, 66, 73, 100, 318 and 320, and physiologically tolerable salts thereof.

As previously mentioned, a number of compounds of formula (I) have been found to be excellent mixed inhibitors in that they inhibit both the serine proteases Factor Xa and thrombin. Such mixed inhibitors are preferably based on the formula (L)

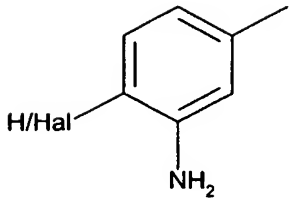


(L)

wherein R' represents

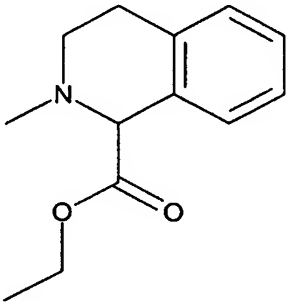


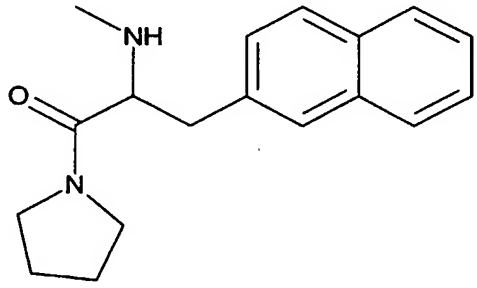
or

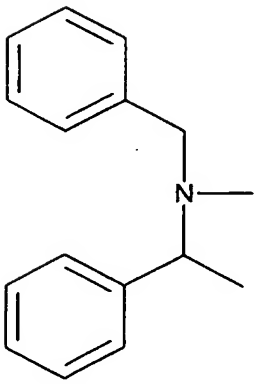


X_3 represents hydrogen or a polar group such as amino or $CONH_2$, especially $CONH_2$; and

R" represents a cyclic group bound to the carbonyl by a nitrogen atom or an optionally substituted group of formula

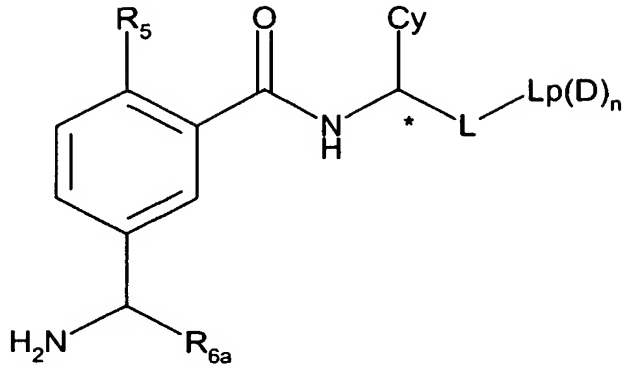






A group of compounds of particular interest for use as

tryptase inhibitors is that of formula



in which:

L-Lp(D)$_n$ represents CO-L$_x$;

R_5 represents amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen;

R_{6a} represents hydrogen or methyl;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, hydrazido, alkylsulphonamido, alkylamino-sulphonyl, aminosulphonyl, haloalkoxy, and haloalkyl;

each R_{1c} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

L_x is a mono or bicyclic group bound to the carbonyl via a pendent nitrogen atom or nitrogen atom which forms part of the mono or bicyclic ring;

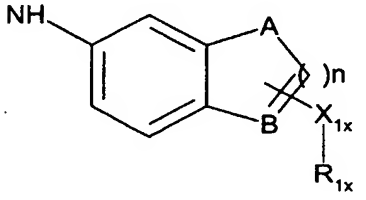
or a physiologically tolerable salt thereof, e.g. a halide, phosphate or sulphate salt or a salt with ammonium or an organic amine such as ethylamine or meglumine.

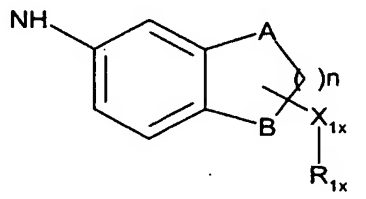
It will be appreciated that when L_x is bound to the carbonyl via a pendant nitrogen, the group CO-L_x corresponds with the group L-Lp(D)$_n$ in which L is CONH and Lp is a mono or bicyclic group. When Lx is bound to the carbonyl via a nitrogen that forms part of the mono or bicyclic ring, the group CO-Lx corresponds with the group L-Lp(D)$_n$ in which L is CO and Lp is a mono or bicyclic group containing a nitrogen atom in the ring and bound to L via this nitrogen.

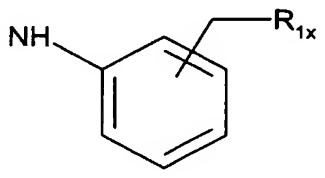
It is believed that an aminomethyl group positioned on the 3 position of the phenyl ring will give rise to excellent binding within the S1 binding pocket of tryptase. Without wishing to be limited by theory it is believed that the presence of a hydrogen bond donating group attached to the phenyl group will be essential for successful inhibition of tryptase.

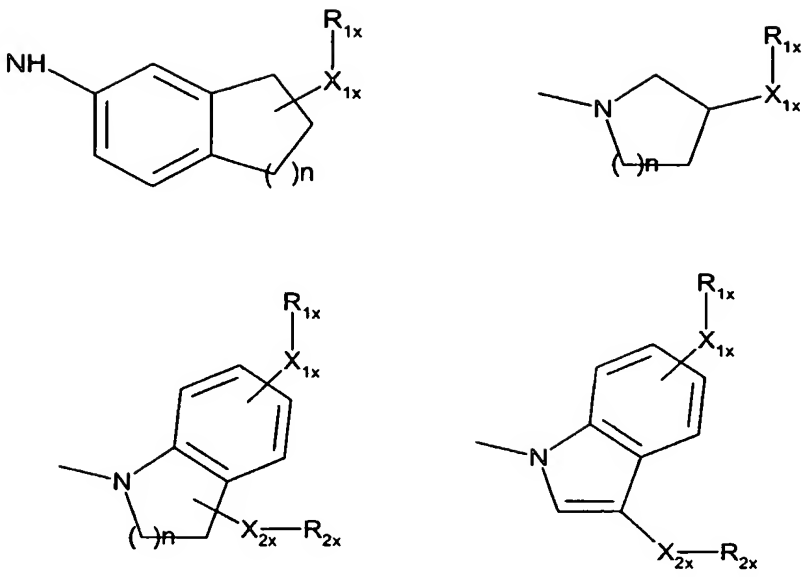
R_5 and R_6 are both preferably hydrogen.

Most preferably the Lx group comprises









wherein:

A and B are independently chosen from NH, N, O, S, CH, CH_2;

X_{1x} and X_{2x} are independently chosen from $(CH_2)_m$, $(CH_2)_mCH=CH(CH_2)_p$, $CO(CH_2)_m$, $NH(CH_2)_m$, $NHCO(CH_2)_m$, $CONH(CH_2)_m$, $SO_2NH(CH_2)_m$, $NHSO_2(CH_2)_m$;

n is 1 or 2;

m is 0 to 2;

p is 0 to 2;

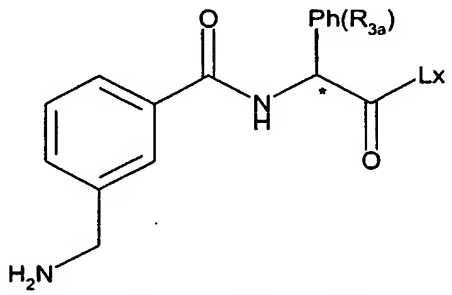
R_{1x} and R_{2x} are independently chosen from hydrogen, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, oxo, heterocyclo optionally substituted by R_{3x}, cycloalkyl optionally substituted by R_{3x} or aryl optionally substituted by R_{3x}; and

R_{3x} is hydrogen, alkoxy, alkyl, amino, hydroxy, alkoxy, alkoxycarbonyl, halo, cyano, nitro, thiol, sulphonyl, or sulphenyl.

Examples of heterocyclic R_{1x} and R_{2x} groups are piperidine, piperazine and pyrrolidine.

The cyclic group attached to the alpha atom is preferably an optionally R_{3a} substituted phenyl.

Thus, one group compounds of formula (I) of interest as tryptase inhibitors are those of formula (II)



* the alpha atom

II

wherein Lx is as hereinbefore defined. It is envisaged that especially preferred Lx groups will be those in which a cyclic or bicyclic ring is substituted by hydrogen bond donating and/or acceptor groups.

The compounds of formula (I) may be prepared by conventional chemical synthetic routes or by routes as illustrated by the following examples, e.g. by amide bond formation to couple the aromatic function to the alpha atom and to couple the lipophilic function to the alpha atom. Where the alpha atom is a carbon, the cyclic group-alpha atom combination may conveniently derive from an alpha amino acid with the aromatic deriving from for example an acid derivative of a compound based on R_2, e.g. o-amino-benzoic acid or aminomethylbenzoic acid. Amide formation from such reagents (in which any amino or hydroxyl function (especially in an aminomethyl group) may if desired be protected during some or all of the synthesis steps) yields a compound of formula (V).

R_2-CONH-CH(Cy)-COOH (V)

(where Cy and R_2 are as defined above).

Prior to reaction the amino group in an aminoalkyl group should be protected by an appropriate protecting group e.g. Boc, Z, Fmoc or Bpoc. The use of protecting groups is described in McOmie, "Protective Groups in Organic Chemistry", Plenum, 1973 and Greene, "Protective Groups in Organic Synthesis", Wiley Interscience, 1981.

The lipophilic group (and optionally simultaneously the hydrogen bond donor) may then conveniently be introduced by reaction of a compound of formula (V) (or another analogous carboxylic acid) optionally after transformation into an activated form, e.g. an acid chloride or active ester, with a lipophilic group carrying an amine, hydroxylamine, hydrazine or hydroxyl group, e.g. to produce compounds with linkages of -CO-NR_{1d}-, -CO-NR_{1d}-O-, -CO-NR_{1d}-NR_{1d}- and -CO-O- from the alpha atom (where it is a carbon) to the lipophilic group. Cyclisation can be base induced via nucleophilic attack of the alpha atom on a leaving group on the active side chain. If necessary the amide linkage can be reduced using an appropriate reducing agent employing the necessary protection depending on whether concurrent reduction of the carboxylic acid moiety is also desired. Alternatively a compound of formula V or another analogous carboxylic acid may be transformed into an alcohol by reaction with isobutylchloroformate and reduction with sodium borohydride.

Such an alcohol, e.g. of formula VI

R_2 - CONH - CH(Cy)CH_2OH (VI),

can be reacted to introduce the lipophilic group by reactions such as:

alkylation with an alkyl halide in the presence of a base;

under Mitsunobu conditions, such as reaction with diethyl azodicarboxylate/triphenylphosphine and a hydroxylated aryl compound;

by reaction with an activated carboxylic acid (e.g. an acid chloride) or with a carboxylic acid and diethylazodicarboxylate/triphenylphosphine;

by reaction with an isocyanate; and

by treatment with methanesulphonyl chloride or trifluoromethanesulphonic anhydride and reaction with an amine, or with a thiol optionally followed by oxidation, e.g. with potassium metaperiodate or hydrogen peroxide.

Alternatively, the reactions described above may be performed on a corresponding compound of formula (VI) in which R_2 is replaced with a protecting group, such as t-butoxycarbonyl (Boc), followed by deprotection and introduction of the group R_2.

In this way compounds with linkages of $-CH_2-O-$, $-CH_2-O-CO-$, $-CH_2-O-CO-NR_{1d}-$, $-CH_2-NR_{1d}-$, $-CH_2-S-$, $-CH_2-SO-$ and $-CH_2-SO_2-$ between the alpha carbon and the lipophilic group may be produced.

Alternatively the alcohol can be oxidized to form a corresponding aldehyde (e.g. by oxidation with manganese dioxide or DMSO/oxalyl chloride or DMSO/SO_3 or Dess-Martin reagent) which may be reacted to introduce the lipophilic group by reactions such as:

reaction with Wittig reagents or Horner-Emmons reagents, optionally followed by reduction of the resulting carbon:carbon double bond using H_2/Pd-carbon;

reaction with an organometallic, eg a Grignard reagent, optionally followed by reaction on the resulting hydroxyl group, such as oxidation (eg with MnO_2, DMSO/oxalyl chloride or Dess-Martin reagent), alkylation (eg with an alkyl halide in the presence of a base in a solvent such as DMF), arylation (eg with diethylazo dicarboxylate/triphenyl phosphine and a hydroxyaryl compound), ester formation (eg with an acid chloride or with a carboxylic acid and diethylazido dicarboxylate/triphenyl phosphine), or carbamate formation (eg with an isocyanate);

by reaction with an amine followed by reduction, e.g. with sodium cyanoborohydride;

by reaction with a hydrazine; or

by reaction with a carbazide.

In this way compounds with linkages of $-CH=CR_{1d}-$, $-CH_2-CHR_{1d}-$, $-CHOH-$, $-CHR_{1d}-O-$, $-CHR_{1d}-O-CO-$, $-CHR_{1d}-O-CO-NR_{1d}-$, $-CO-$, $-CH_2-NR_{1d}-$, $-CH=N-NR_{1d}-$ and $-CH=N-NR_{1d}-CO-NR_{1d}-$ between the alpha carbon and the lipophilic group may be produced.

The transformation of alcohol to amine referred to above may be used to produce an amine reagent for lipophilic group introduction, e.g. a compound

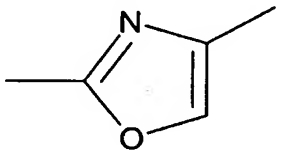
$$R_2-CONH-CH(Cy)-CH_2-NR_{1d}H.$$

Such an amine reagent may be reacted to introduce the lipophilic group, e.g. by acylation with an acid halide or activated ester, by reaction with isocyanate, by reaction with an isothiocyanate, or by reaction with a sulphonyl chloride. In this way compounds with linkages of $-CH_2NR_{1d}-CO-$, $-CH_2-NR_{1d}-CO-NR_1-$, $-CH_2NR_{1d}-CS-NR_{1d}-$ and $-CH_2NR_{1d}-SO_2-$ between the alpha carbon and the lipophilic groups may be produced.

The transformation of acid to amide referred to above may be used to produce an amide reagent for introduction of the lipophilic group, e.g. a compound

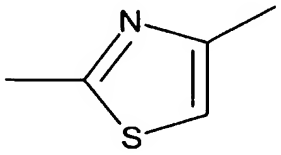
$$R_2\text{-}CONH\text{-}CH(Cy)\text{-}CON(R_{1d})_2.$$

Such amides may be reacted to introduce lipophilic groups, e.g. by reaction with a haloketone (e.g. phenacyl bromide). This provides a linkage

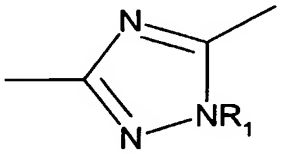


from alpha carbon to lipophilic group.

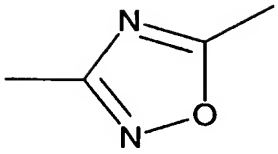
Analogously the amide may be transformed to a thioamide by reaction with Lawesson's reagent and then reacted with a haloketone to form a linkage



The amide reagent may likewise be transformed to a nitrile reagent by dehydration, e.g. with trifluoroacetic anhydride. The nitrile reagent may be reacted with hydrazine then with acyl halide and then cyclized, (e.g. with trifluoroacetic anhydride) to produce a linkage



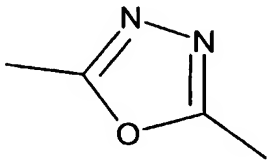
Alternatively it may be treated with hydroxylamine then reacted with acyl halide and cyclized (e.g. with trifluoroacetic anhydride) to produce a linkage



The hydrazide produced by reaction of a carboxylic acid reagent with hydrazine discussed above may likewise be used as a reagent for lipophilic group introduction, e.g. as a compound of formula

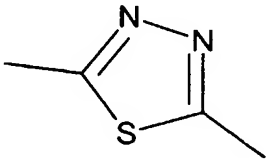
$$R_2\text{-}CONH\text{-}CH(Cy)\text{-}CO\text{-}NR_1\text{-}N(R_{1d})_2.$$

Thus the hydrazide reagent can be reacted with an acyl halide and cyclized, e.g. with trifluoroacetic anhydride to yield a linkage

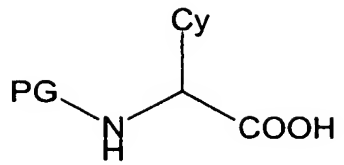


or reacted with an acyl halide or an isocyanate to yield linkages $-CO\text{-}NR_{1d}\text{-}NR_{1d}\text{-}CO-$ and $-CO\text{-}NR_{1d}\text{-}NR_{1d}\text{-}CO\text{-}NR_{1d}-$ respectively.

Alternatively the hydrazide may be transformed by reaction with Lawesson's reagent and then reacted with an acyl halide and cyclized (e.g. with trifluoroacetic anhydride) to produce the linkage



An alternative route to these compounds is to carry out any of the above chemical reactions to incorporate the lipophilic group (and optional H bond donor) into a protected intermediate such as a compound of formula (VII).



PG = Protecting group

The protecting group may then be removed before coupling of the for example o-amino benzoic acid (optionally protected).

The protection of amino and carboxylic acid groups is described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxy protecting groups include C_1-C_6 alkyl groups such as methyl, ethyl, *t*-butyl and *t*-amyl; aryl(C_1-C_4)alkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and *t*-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine protecting groups (PG) include acyl groups, such as groups of formula RCO in which R represents C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl C_{1-6} alkyl, phenyl, C_{1-6} alkoxy, phenyl C_{1-6} alkoxy, or a C_{3-10} cycloalkoxy, wherein a phenyl group may be optionally substituted, for example by one or two of halogen, C_1-C_4 alkyl and C_1-C_4 alkoxy. Preferred amino protecting groups include benzyloxycarbonyl (CBz), t-butoxycarbonyl (Boc) and benzyl.

α-Amino acids of formula (VII) which are not commercially available can be synthesized by methods known in the art, for example as described in "Synthesis of Optically Active α-Amino Acids" by Robert M. Williams

(Pergamon Press, 1989) and "Asymmetric Synthesis of ArylGlycines", Chem. Rev. 1992, 889-917.

Compounds of the type (VII) made be prepared (for example) by one or more of the following methods.

(i) from aryl or heteroaryl aldehydes via the Strecker synthesis or modifications thereof, via Bucherer-Bergs hydantoin synthesis, or via the Ugi methodology (Isonitrile Chemistry, Ugi I. Ed.; Academic: New York, 1971; pp145-199) with removal and replacement of protecting groups;

(ii) from styrenes via Sharpless methodology (J. Am. Chem. Soc. 1998,120, 1207-1217)

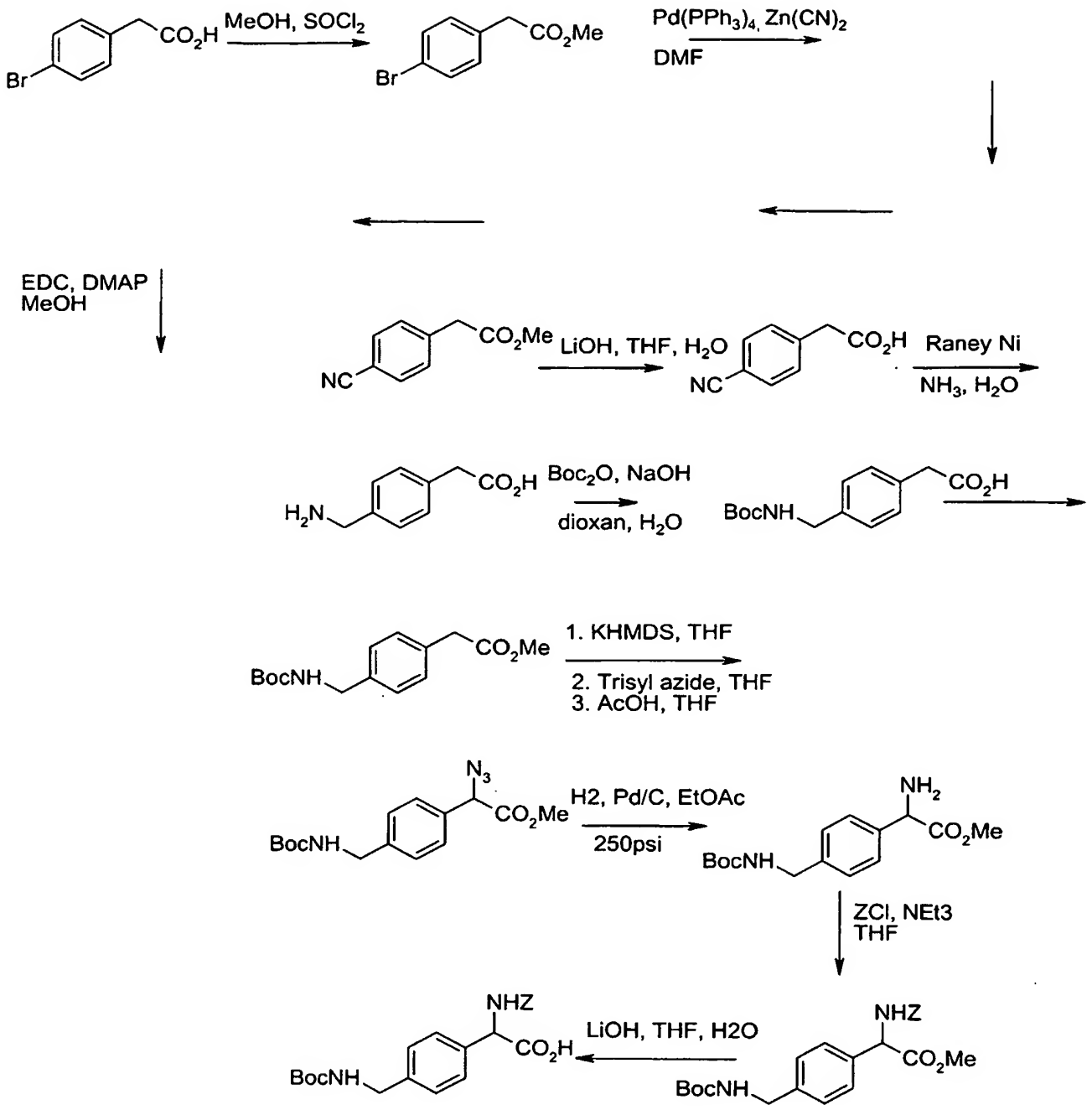
(iii) from aryl boronic acids via Petasis methodology (Tetrahedron, 1997, 53, 16463-16470) with removal and replacement of protecting groups;

(iv) from aryl and heteroaryl acetic acids - via Evan's azidation (Synthesis, 1997, 536-540) or by oximation, followed by reduction and addition of protecting groups; or

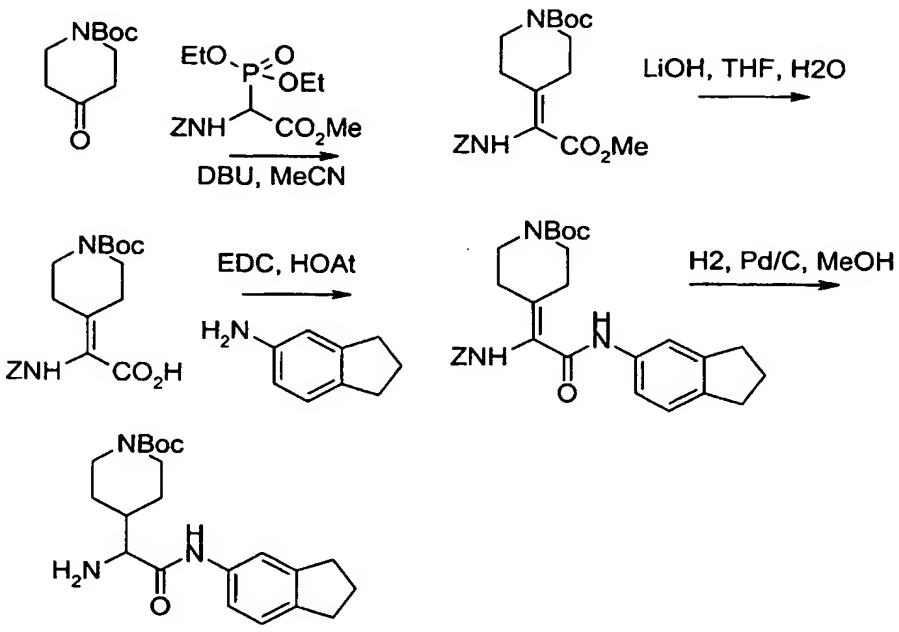
(v) from existing aryl glycines by manipulation of functional groups, for example, alkylation of hydroxy groups, palladium assisted carbonylation of triflates derived from hydroxy groups and further manipulation of the carboxylic esters to give carboxylic acids by hydrolysis, carboxamides by activation of the carboxylic acid and coupling with amines, amines via Curtius reaction on the carboxylic acid or

(vi) from aliphatic, carbocylic and non-aromatic heterocyclic aldehydes and ketones using a Horner-Emmons reaction with N-benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (Synthesis, 1992, 487-490).

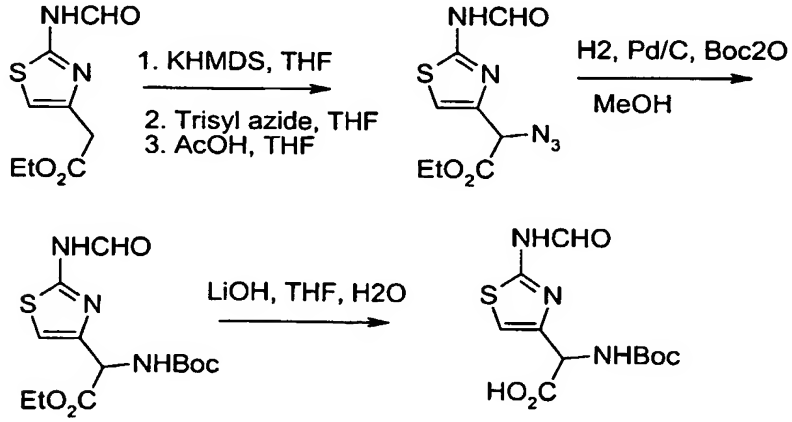
Examples of synthetic routes are shown below:



Synthesis of protected 4-piperidylglycine

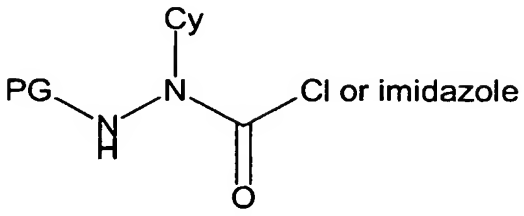


Synthesis of protected 2-aminothiaz-4-ylglycine



A starting reagent for lipophilic group introduction where the alpha atom is nitrogen may be produced for example by reaction of a beta protected hydrazine (such protection to be chosen as to be compatible with the subsequent reagents to be employed) with phosgene, diphosgene,

triphosgene or N,N'carbonyl diimidazole to give a reactive compound of the type:



PG = Protecting group

This intermediate may be used as has been described above for the carboxylic starting reagents where the alpha atom is carbon.

Removal of the protecting group by standard methods and coupling with an activated aryl carboxylic acid will give compounds of the type

$$R_2\text{-CONH-N(Cy)-L-Lp(D)}_n$$

(where R_2, X, Y, Cy, L, Lp and D are as defined above).

Thus the compounds of formula (I) may be prepared by a process which comprises coupling a lipophilic group to a compound of formula (VIII)

$$R_2\text{-(X)}_2\text{-Y(Cy)-}Z_1 \qquad \text{(VIII)}$$

(wherein R_2, X, Y and Cy are as defined above and Z_1 is a reactive functional group), and optionally subsequently coupling a hydrogen bond donor group to said lipophilic group.

Instead of introducing the group L-Lp(D)_n as the final stage process step, the compounds of formula I may alternatively be prepared by a process in which the group R_2 is introduced in the final process step.

Thus the compounds of formula (I) may also be prepared by a process which comprises coupling a lipophilic group to a compound of formula (IX)

$$Z_2\text{-}Y(Cy)\text{-}L\text{-}Lp(D)_n \qquad (IX)$$

(wherein Y, Cy, L, Lp D, and n are as defined above and Z_2 is HX or a reactive functional group), or a protected derivative thereof, with a compound of formula (X)

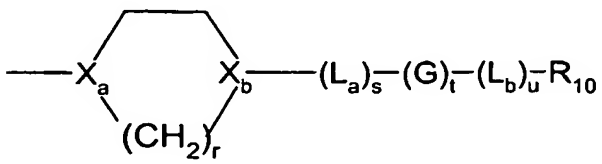
$$R_2\text{-}\ Z_3$$

(wherein R_2 is as defined above and Z_3 is XH or an appropriate reactive group), or a protected derivative thereof, followed if necessary by the removal of any protecting groups.

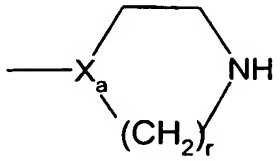
Thus, for a compound of formula I in which X-X represents CONH, a compound of formula (IX) in which Z_2 is H_2N may be reacted with a compounds of formula (X) in which Z_3 is COOH or a reactive derivative thereof, such as a acyl halide or an anhydride, for example as described in the Examples herein.

Where the lipophilic group Lp comprises more than one group, it may generally be formed by coupling these groups together at an appropriate stage in the preparation of the compound of formula I using conventional methods or as descibed in the Examples.

For a compound of formula I in which Lp comprises an azacycloalkyl or diazacycloalkyl group of formula

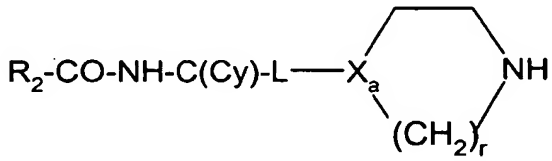


in which X_b is N and each of s and u is 0, alkylating the amino group of a corresponding compound in which the corresponding residue is of formula



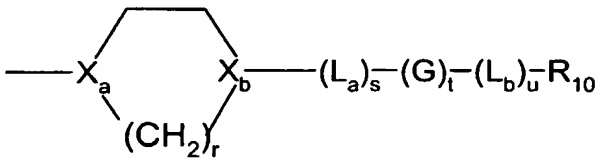
using a conventional alkylating method. The alkylation may be carried out using any conventional method; however, generally preferred is a reductive alkylation using the appropriate aldehyde or ketone, for example as described in the Alkylation Methods in the Examples.

Thus, a particular starting material for the alkylation is one of formula

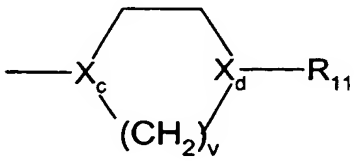


in which X_a is N and L is CO or X_a is CH and L is CONH, $CONHCH_2$ or CH_2NHCO.

For a compound of formula I in which Lp comprises an azacycloalkyl or diazacycloalkyl group of formula

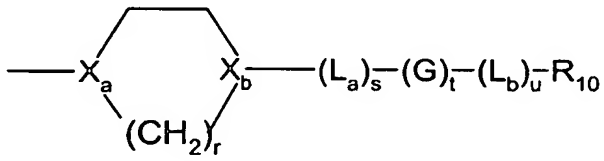


in which R_{10} is a group of formula

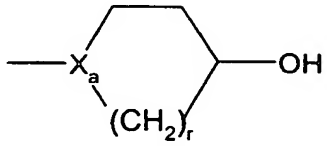


in which X_d is N and R_{11} is (1-6C)alkyl, alkylating the amino group of a corresponding compound of formula I in which R_{11} is hydrogen using a conventional method. Generally preferred is a reductive alkylation using the appropriate aldehyde or ketone, for example as described in the Alkylation Methods in the Examples.

For a compound of formula I in which Lp comprises an azacycloalkyl or diazacycloalkyl group of formula

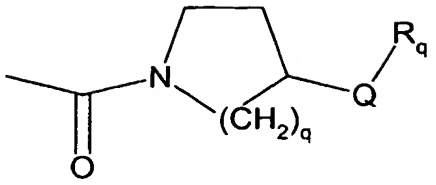


in which X_b is CH and $(L_a)_s$-$(G)_t$-$(L_b)_u$ is O and R_{10} is phenyl or pyridyl, coupling a corresponding compound containing a group of formula

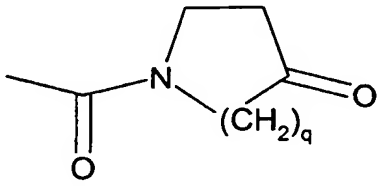


with phenols or 3-hydroxypyridine using Mitsunobu conditions, eg. DEAD (diethyl azodicarboxylate) /Ph_3P or 2-triphenylphosphonium 4,4-dimethyl-tetrahydro-1,2,5-thiadiazole to give aryloxy or 3-pyridoxy substituted piperidines or pyrrolidine. Alternatively the hydroxy group may be reacted with sodium hydride and 2-chloro or 4-chloropyridine to give 2-pyridoxy or 4-pyridoxy substituted piperidines or pyrrolidines.

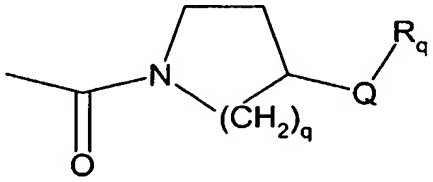
For a compound of formula I in which -L-Lp$(D)_n$ is



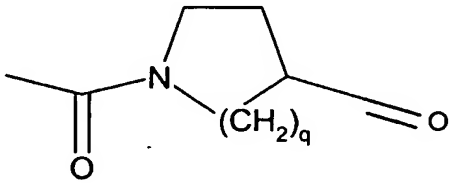
in which Q is a direct bond, reductively alkylating an amine of formula H-Q using a corresponding compound in which the corresponding residue is a ketone of formula



For a compound of formula I in which -L-Lp(D)$_n$ is



in which Q is methylene, reductively alkylating an amine of formula H-NR_aR_b using a corresponding compound in which the corresponding residue is an aldehyde of formula



For example, methyl 1-acetyl-3-formylindole-6-carboxylic acid may be converted to the 3-formate by the method of Merour et al (Synthesis, 1994, 411) and then reacted with trimethyl orthoformate to give methyl 1-acetyl-3-methoxyindole-6-carboxylate which is then hydrolysed to methyl 1-acetyl-3-methoxyindole-6-carboxylate.

5-Fluoroindole-6-carboxylic acid may be prepared from 4-fluoro-3-methoxyaniline by the following method. 4-Fluoro-

3-methoxyaniline is treated with glyoxal-1,1-dimethyl acetal and then hydrogenated over Pd/C. The product is N-protected with methanesulphonyl chloride and then cyclised using titanium tetrachloride in toluene. Demethylation with BBr_3 to the phenol followed by reaction with triflic anhydride and then palladium carbonylation in methanol gives the methyl ester, which is then converted to 5-fluoro-1-methanesulphonylindole-6-carboxylic acid by hydrolysis with lithium hydroxide. This 'benzoyl' component may be reacted as previously described and deprotected by hydrolysis with sodium hydroxide at 100°C.

The compounds of formula (I) may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or vasculature or transdermally. The compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. Preferably the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

The following are examples of pharmaceutical compositions of compounds of formula (I) or physiologically tolerable salts thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 60 mg of active ingredient are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

It is believed that the compounds of the invention will have excellent oral bioavailability.

Thus the compounds of formula (I) and their physiologically tolerable salts will generally be adminstered to a patient in pharmaceutical composition which

comprises a serine protease inhibitor of formula (I) together with at least one pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may also optionally comprise at least one further antithrombotic and/or thrombolytic agent.

The dosage of the inhibitor compound of formula (I) will depend upon the nature and severity of the condition being treated, the administration route and the size and species of the patient. However in general, quantities of from 0.01 to 100 μmol/kg bodyweight will be administered.

All publications referred to herein are hereby incorporated by reference.

The following non-limiting Examples illustrate the preparation of compounds of formula (I) for use as serine protease inhibitors according to the invention.

Examples - Part 1

Experimental

Abbreviations used follow IUPAC-IUB nomenclature. Additional abbreviations are Hplc, high-performance liquid chromatography; DMF, dimethylformamide; DCM, dichloromethane; HAOT, 1-hydroxy-7-azabenzotriazole; HATU, [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate]; Fmoc, 9-Fluorenylmethoxycarbonyl; HOBt, 1-hydroxybenzotriazole; TBTU, 2-(1H-(benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate; EDCI, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DIPEA, diisopropylethylamine; Boc, tertiary butyloxycarbonyl; DIPCI, diisopropylcarbodiimide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TEA, triethylamine; Rink linker, p-[(R,S)-α-[1-(9H-Fluoren-9-yl)methoxyformamido]-2,4-dimethoxybenzyl]phenyl acetic acid; TFA, trifluoroacetic acid; MALDI-TOF, Matrix assisted laser desorption ionisation - time of flight mass spectrometry, RT, retention time. Amino acid derivatives, resins and coupling reagents were obtained, for example, from Novabiochem (Nottingham, UK) and other solvents and reagents from Rathburn (Walkerburn, UK) or Aldrich (Gillingham, UK) and were used without further purification. All solution concentrations are expressed as %Vol./%Vol. unless otherwise stated.

Purification: Purification was by gradient reverse phase Hplc on a Waters Deltaprep 4000 at a flow rate of 50 ml/min. using a Deltapak C18 radial compression column (40 mm x 210 mm, 10-15 mm particle size). Eluant A consisted of aqTFA (0.1%) and eluant B 90% MeCN in aq TFA(0.1%) with gradient elution (Gradient 1, 0 min. 20%B then 20% to 100%